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FINAL REPORT AD
Chemical Study - Synthesis of
Incapacitating Agents
by C. I. Judd, H. A. Leiser,
J. W. LaFrentz, W. K. Hoya
18 October 1964

US Army Edgewood Arsenal
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Lakeside Laboratories,
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Final REPORT

Covering the Period

1 July 1962 to 7 September 1964

Title: Chemical Study - Synthesis of Incapacitating Agents

Prepared By

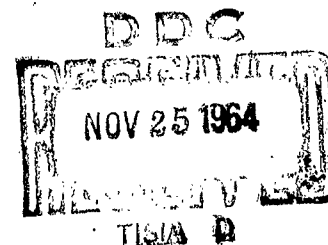
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FOREWARD

The work described in this report was authorized under Project DA-18-108-CML-7121, Chemical Incapacitating Agents (S). This work was started in July, 1962 and completed in September, 1964. The experimental data are contained in notebooks numbered 1029, 1030, 1051, 1054, 1076, 1078, and 1095.

Acknowledgments

Acknowledgments are due to Dr. H. Aaron, the Army Chemical Center, Edgewood Arsenal, Maryland, and the Lakeside Analytical Department for infrared spectral and elemental analyses.

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DIGEST

This report describes the accomplishments with respect to:
(1) the synthesis of new esters of 3-hydroxyquinuclidine; (2) synthesis of new bicyclic aminoalcohols and benzilate esters thereof; (3) synthesis of basic derivatives of 5-substituted dibenzo[a,d]cyclobutenes; and (4) investigations for the resolution of phenylcyclopentylglycolic acid.

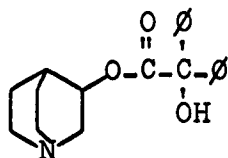
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The observation that certain centrally acting anticholinergic agents caused hallucinations and mental confusion in man¹ and that one compound, 3-quinuclidyl benzilate (1), was particularly potent and long acting² caused us to undertake a synthetic program directed to the preparation of a related series of compounds in order to study the structural requirements for activity. In addition, the program was designed to explore and uncover new structural leads for further synthetic elaboration.



Considering the structural features of 1, it was obvious that there were two major portions of the molecule available for variation, i.e., the aminoalcohol moiety and the acid moiety. Beyond this we felt that the acid moiety could not only be varied structurally, but could also be varied functionally, keeping in mind the general spatial features of the molecule. This concept was well met in the dibenzo[a,d]cycloheptene system. This report will, therefore, describe our work with (1) quinuclidyl esters; (2) bicyclic aminoalcohols and derivatives thereof; (3) dibenzo[a,d]cycloheptene derivatives; and (4) miscellaneous investigations in related fields.

Quinuclidyl Esters

Our first synthetic efforts concerned the preparation of a series of esters which, with one exception, (ACC 7121-17, Table II), were esters of 3-hydroxyquinuclidine. The acids selected for this study followed closely the group described by Pyman³ for his investigations with the tropine esters.

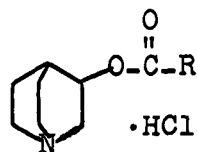
Table I describes a group of aryl and aryl acetic acid esters in this series. With one exception, ACC 7121-18, these esters were formed by the interaction of the appropriate acid chloride and 3-hydroxyquinuclidine.

In contrast to ortho-hydroxybenzoic acid, which readily formed an acid chloride on treatment with thionyl chloride,⁴ the meta and para isomeric acid chlorides were too unstable in our hands to be of synthetic value. We, therefore, utilized the benzyloxy acid chlorides, prepared according to the procedure described by Cavallito and Buck,⁵ for the preparation of compounds ACC 7121-9 and ACC 7121-11.

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Quinuclidyl Esters of Aromatic Acids

TABLE I



ACC 7121	R	m.p. °C
11		186-188°
9		236-237°
5		266-267°
6		245-247°
7		259-261°
12		214-216°
10		199-201°
18		180-181°

These compounds were not only of interest for biological evaluation, but also served as intermediates affording the free hydroxy derivatives, ACC 7121-6 and ACC 7121-7, on catalytic reductive debenzoylation.

The trimethoxybenzoyl and p-chlorophenoxyacetyl derivatives, ACC 7121-12 and ACC 7121-10, were obviously selected because esters of the corresponding acids are well-known centrally acting agents.

Compound ACC 7121-18 was prepared by transesterifying ethyl phenylacetate with 3-hydroxyquinuclidine using aluminum isopropoxide as the catalyst and heating at 120-150°C under reduced pressure.

Table II is a listing of hydroxy alkyl acid esters of 3-hydroxyquinuclidine and intermediates of their preparation.

The most direct approach to the preparation of these compounds was by esterification of the appropriate acid and, indeed, four of the listed compounds were obtained in this manner. The lactate ester, ACC 7121-1, was obtained using a modification of the standard transesterification procedure for compounds of this type⁶ in which aluminum isopropoxide was used as the catalyst in the place of the more conventional sodium alkoxide. In the same manner, the atrolactate, ACC 7121-4 was prepared.

The keto esters, ACC 7121-14 and ACC 7121-15, were prepared without difficulty following the procedure described by Bader.⁷ Hydrogenation of ACC 7121-14 over platinum resulted in the consumption of one mole of hydrogen and the formation of the hydroxy ester, ACC 7121-16.

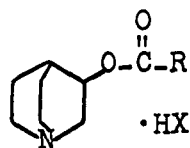
It should be mentioned that the compounds containing a functional grouping other than hydroxyl, ACC 7121-13, ACC 7121-14 and ACC 7121-15 were of primary interest as synthetic intermediates to the desired hydroxy acids.

Attempts to convert the benzoylacetate ACC 7121-15 to the β,β -diphenyl- β -hydroxypropionate, ACC 7121-8, by treatment with metallic phenyl derivatives, e.g. diphenyl cadmium or phenyl lithium, were unsuccessful and, in fact, the reactions failed to take the desired course even in the model system using ethyl benzoylacetate as the keto ester. Success was achieved in the preparation of the desired ester, however, using the procedure described by Hauser⁸ which involved the condensation of 3-quinuclidyl acetate with benzophenone in liquid ammonia containing sodamide.

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Quinuclidyl Esters of Hydroxy Acids and Intermediates Thereof

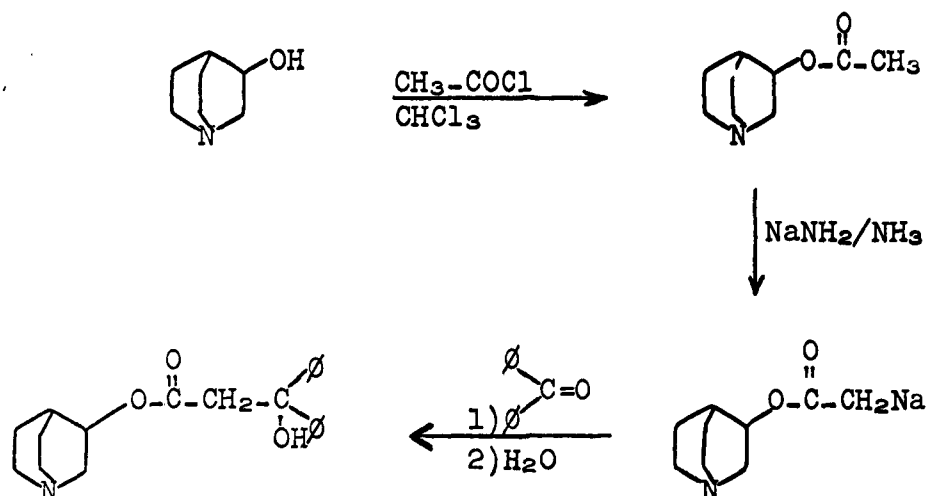
TABLE II



ACC 7121	R	X	m.p. °C
1	$\begin{array}{c} \text{H} \\ \\ \text{CH}_3 - \text{C} - \\ \\ \text{OH} \end{array}$	Free Base	73-76°
4	$\begin{array}{c} \phi \\ \\ \text{CH}_3 - \text{C} - \\ \\ \text{OH} \end{array}$	Cl	244-245°
8	$\begin{array}{c} \phi \\ \\ \phi - \text{C} - \text{CH}_2 - \\ \\ \text{OH} \end{array}$	Cl	243°
13	$\begin{array}{c} \text{H} \\ \\ \phi - \text{C} - \\ \\ \text{Br} \end{array}$	Br	183-185°
14	$\text{CH}_3 - \text{C}(\text{O}) - \text{CH}_2 -$	Cl	177-178°
15	$\phi - \text{C}(\text{O}) - \text{CH}_2 -$	Cl	158-159°
16	$\begin{array}{c} \text{H} \\ \\ \text{CH}_3 - \text{C} - \text{CH}_2 - \\ \\ \text{OH} \end{array}$	Cl	155-156°
17		Cl	262°

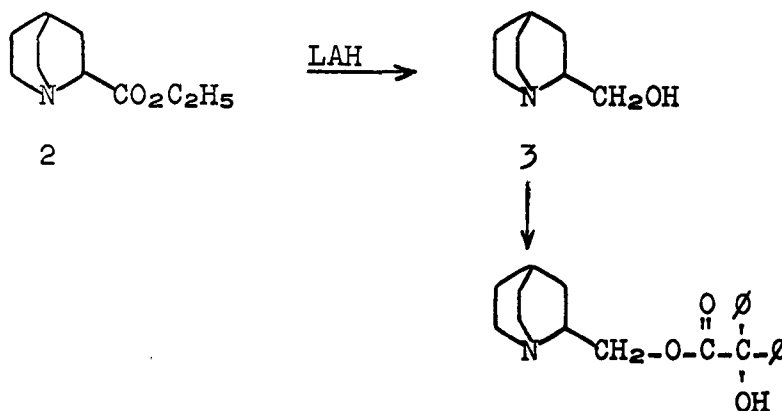
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ACC 7121-3

The 2-quinuclidylmethyl ester, ACC 7121-17, was of particular interest because the compound retained the quinuclidyl amino-alcohol structure, but lacked the rigidity and fixed interatomic relationship between N and O characteristic of the three quinuclidyl esters.



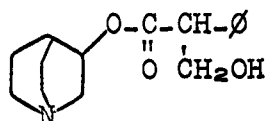
ACC 7121-17

Ethyl 2-quinuclidyl carboxylate (2) was readily available from the procedure of Renk and Grob.⁹ Reduction of 2 with lithium aluminum hydride afforded the carbinol 3 in 76% yield. The boiling range was essentially the same as that obtained by Prelog¹⁰ using sodium and alcohol reduction.

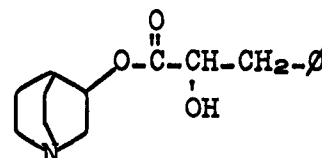
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Esterification of 3 was accomplished using the sodium methylate catalysis technique of Biel⁶ affording the benzilate ester, ACC 7121-17, in 36% yield.

Numerous attempts to prepare two compounds, 4 and 5, were unsuccessful. This lack of synthetic success has been ascribed, in part, to the lability of these acids and esters with respect to the ease with which they can dehydrate under a variety of reaction



4

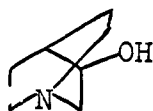


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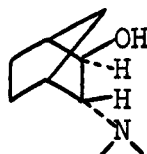
conditions.

Bicyclic Aminoalcohols and Derivatives

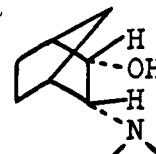
One of the most interesting and perhaps the most important aspect of these studies involved an investigation of the N-O spatial relationship in fixed systems and the affect of varying distance on the activity of the resultant esters. The interatomic distances between N and O in 3-quinuclidinol (6), coincides exactly (as determined from a study of Dreiding Models) with that of the bicyclic aminoalcohols wherein the hydroxyl and amino group are fixed in a trans relationship (7a).



6



7a

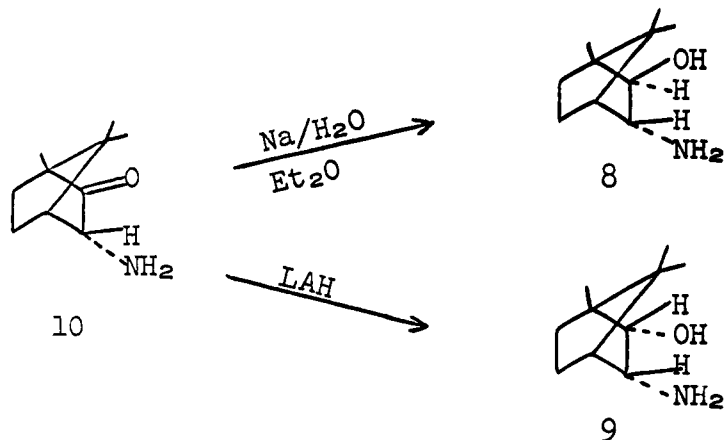


7b

In contrast, when these groups are in a cis (7b) relationship, the interatomic distances are significantly less. It seemed logical, therefore, that if both the ester function and the amine function are involved in bonding to a receptor surface which possesses specific stereochemical requirements, esters derived from these bicyclic systems would show marked differences in activity. With these thoughts in mind, we undertook an investigation into the chemistry of these interesting compounds. The borneol and isoborneol amines were selected as a starting point since much is known about the chemistry of these compounds and they, therefore, served well as working model systems. The preparation of two isomeric aminoborneols has been described by Duden and Macintyre.¹¹

α -Aminoborneol was determined to have the trans configuration 8, and β -aminoborneol the cis-endo configuration 9.

The procedure described by Duden¹¹ readily afforded d,1- α -aminocamphor 10. Reduction of 10 with sodium and wet ether yielded a product which was assigned the trans configuration corresponding



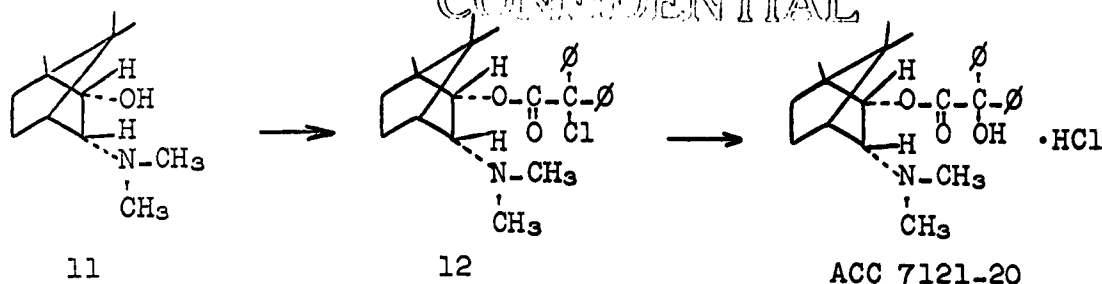
to α -aminoborneol 8. Similarly lithium aluminum hydride reduction afforded the cis- β -product 9. These assignments were made on the basis of analogy with the d-camphor system.^{12,13}

VPC analysis of these products indicated that they were each seriously contaminated (about 25%) with the other isomer. In view of this, the stereochemical assignments made for these aminoalcohols must be accepted with considerable reservation until studies are conducted on VPC pure isomers. Such studies were felt to be beyond the scope of this investigation since our basic interest was in the norborneol system. However, the stereochemistry of the products obtained in our investigation were assigned on the basis of existing literature evidence, and would, therefore, be subject to change if new data becomes available.

The α and β -aminoborneols were converted to the N,N-dimethyl derivatives using either Eschweiler-Clarke modification of the Leukart Reaction or successive formylation and reduction with lithium aluminum hydride. The latter procedure had the advantage that the product methylated amines were obtained uncontaminated with the unmethylated precursors.

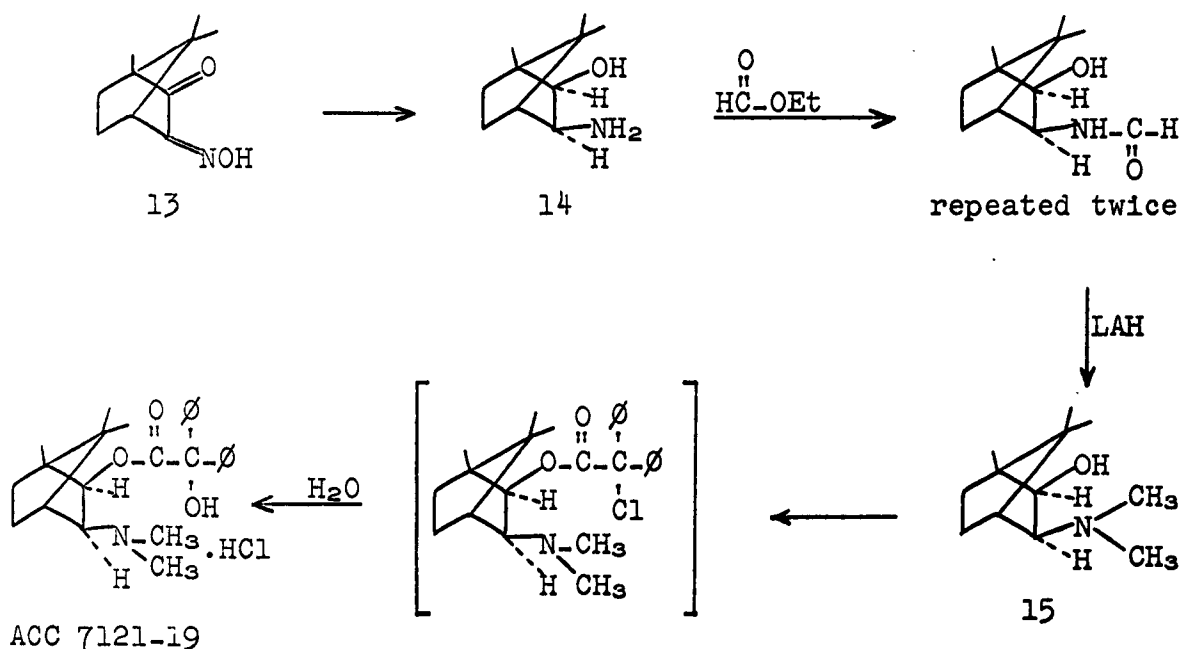
Attempts to esterify the tertiary aminoalcohols by transesterifying methyl benzilate were unsuccessful. However, the amine assigned the cis-endo configuration 11 formed the ester on treatment with diphenylchloroacetyl chloride 12 and this on hydrolysis yielded the benzilate ACC 7121-20.

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Several attempts to carry out the same sequence of reactions with the trans isomer were unsuccessful.

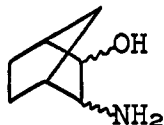
A third isomeric aminoalcohol, 14, that had not been previously reported, was obtained by total reduction of the oximino ketone 13 with lithium aluminum hydride. This isomer exhibited a single elution band on VPC analysis with a retention time that was different than either 8 or 9. Conversion to the N,N-dimethyl derivative was accomplished by successive formylation and lithium aluminum hydride reduction. The product thus obtained when subjected to dilute solution hydrogen bonding studies in the infrared exhibited only bonded O-H---N.* Since this is acceptable evidence for the existence of a cis-relationship, the stereochemistry can be assigned as cis-exo, 15. Conversion of 15 to the benzilate, ACC 7121-19, was readily accomplished via the diphenylchloroacetyl intermediate as described for ACC 7121-20.



*We are grateful to Dr. H. Aaron, Army Chemical Center, Edgewood Arsenal, Maryland for this determination.

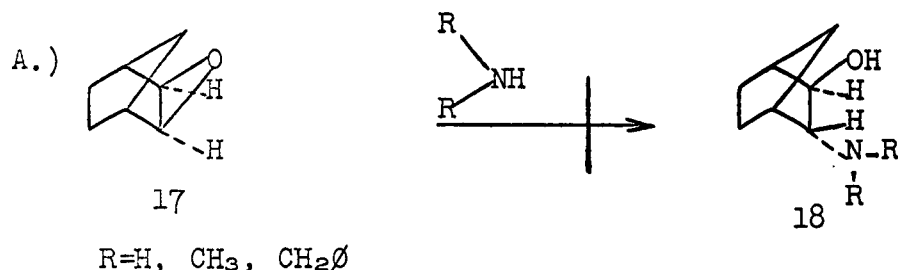
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Since the focal point of our interest in the bicyclic amino esters was on the norborneolamine system, considerable effort was expended exploring synthetic routes to these compounds. Specifically our attention was first drawn to the system exemplified by 16, in which the amino and hydroxyl functions were attached directly to the ring.

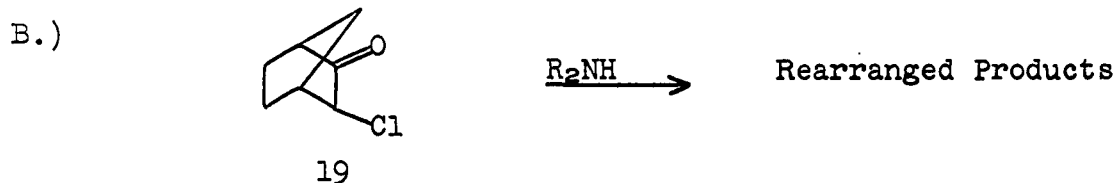


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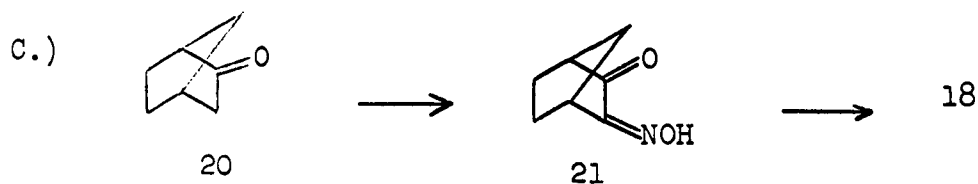
The synthetic methods investigated are listed below:



The possibility of opening the epoxide ring of 17 with amines was explored in depth since this would have provided a convenient route to the desired aminoalcohols of predictable configuration. *p*-Chloroperbenzoic acid oxidation of norbornylene readily afforded the epoxide, 17, with established *exo* configuration.^{14,15} Treatment with secondary amines, i.e. dimethylamine and dibenzylamine, under a variety of conditions of temperature and pressure failed to yield any of the desired aminoalcohols. Sodium amide in liquid ammonia was equally unsuccessful. In each case, the starting material was recovered in high yield as the only identifiable product. Acid catalysts in the form of amine salts were avoided in order to minimize the possibility of skeletal rearrangements. This lack of reactivity can probably best be explained by steric resistance to *endo* nucleophilic attack on the epoxide carbons.

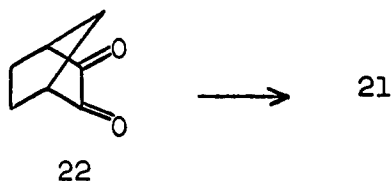


Treatment of α -chloronorcamphor,¹⁶ 19, with ethanolic dimethylamine afforded no significant amount of 18. Only neutral unidentified materials were obtained.

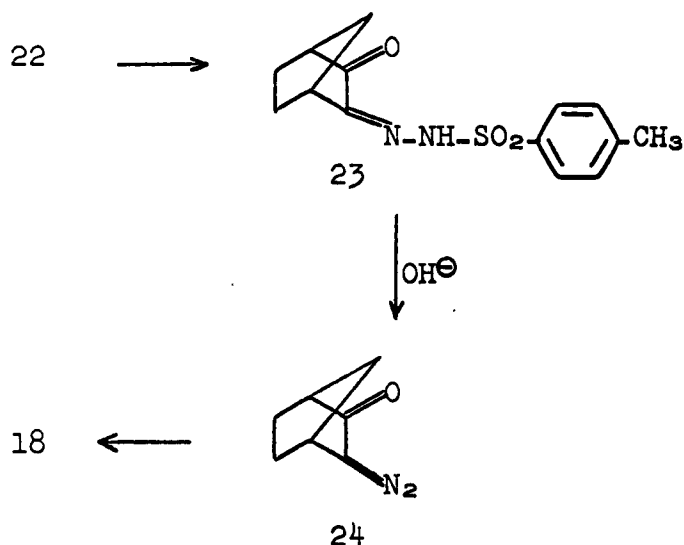


Using as a precedent the synthetic route successfully employed for the borneolamines, the nitrosation of norcamphor, 20, was investigated. All attempts to isolate and identify the oximino ketone, 21, from either base catalyzed nitrosations employing isoamyl nitrite as nitrosating agent or using nitrous acid generated in acetic acid were unsuccessful. Further, all attempts to isolate the desired aminoalcohols, 18, by direct reduction of the crude nitrosation reaction product were abortive.

Another considered possibility for generation of 21 involved monoxime formation from norcamphor quinone, 22, which was available from selenium dioxide oxidation of norcamphor according to

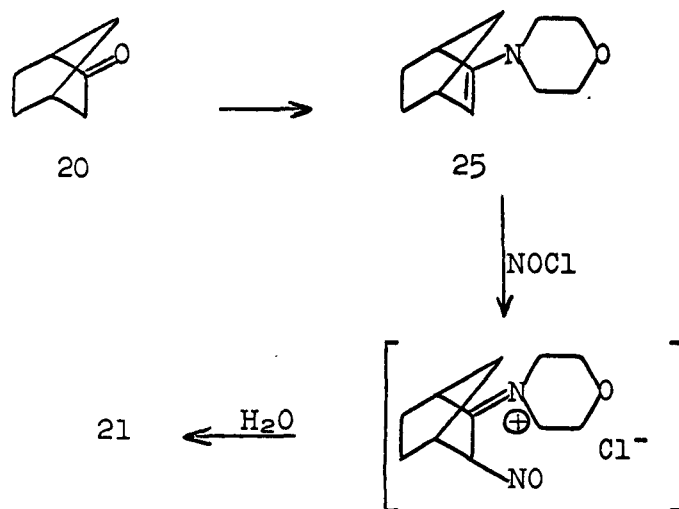


the procedure of Alder.¹⁷ A related procedure involved the formation of the sulfonyl hydrazone, 23, and base catalyzed decomposition to yield the diazoketone, 24,¹⁸ which it was felt could be reduced



without difficulty to the desired product, 18. These approaches, although unsuccessful, were not explored in depth and in the opinion of the authors still represent approaches worthy of further effort. Our lack of success most probably can be attributed to the poor quality of the quinone we obtained from the selenium dioxide oxidation.

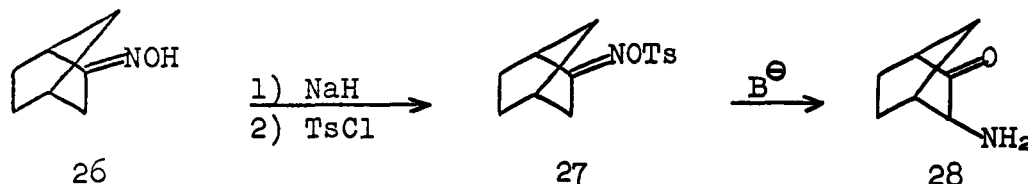
D.) A further modification of the basic concept of functionalizing the activated methylene of norcamphor with a reducible nitrogen containing group, involved the formation of the morpholine enamine, 25, treatment of 25 with nitrosyl chloride and hydrolysis to the oximino ketone 21. The soundness of this synthetic approach was supported by



the fact that during our investigation, Metzger reported on the addition of nitrosyl chloride to enamines.¹⁹

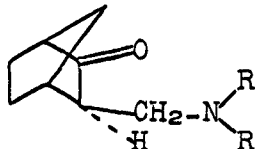
Unfortunately, in our hands the nitrosyl chloride addition did not take the desired course. We were never able to isolate the desired oximino ketone, 21. Again our attempts to produce a basic product by reduction of the crude reaction mixture were unsuccessful. It is felt that this scheme is worthy of a more determined effort, since so new an approach to compounds of this type should not be passed over lightly. This possibility will definitely receive further consideration in our laboratories in the future.

E.) At the conclusion of this contract period, we were considering the Neber reaction²⁰ as a possible synthetic tool to open up a route to the aminoketone, 28. Treatment of norcamphor with hydroxylamine



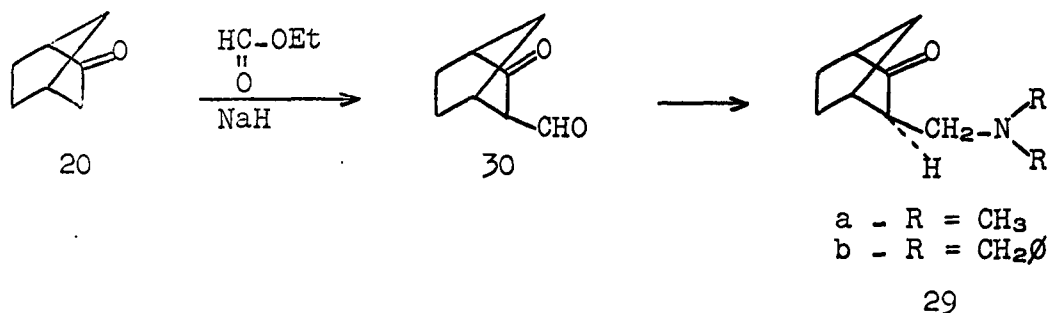
in the presence of excess sodium hydroxide readily afforded the oxime 26. The O-tosylate, 27, was satisfactorily synthesized by treatment of the oxime anion with tosyl chloride.²¹ Whether the rearrangement to 28 will occur on treatment with alkoxide is still speculative. This will be explored as part of the Lakeside research program.

While our work on the bicyclic system was in progress, a report appeared in the literature that the aminomethyl bicyclic ketones, 29, were active analgetic agents.²² This prompted an expansion



29

of our investigation to include compounds of this type and especially to explore the associated aminoalcohols. We first approached these compounds synthetically through the formyl derivative, 30, which was readily obtained by treatment of norcamphor with ethyl formate in ether or Stelly B using sodium hydride as the catalyst. Reductive



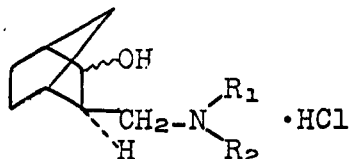
amination of 30 with either dimethylamine or dibenzylamine using hydrogen and a platinum catalyst yielded the aminoketones 29a or 29b in reasonable yield. A more convenient route to these compounds utilized the Mannich reaction which was described in the French Patent literature²³ subsequent to our initial investigation. The N,N-dimethyl derivative, 29a, was prepared via both procedures and the resulting products proved to be identical in every respect when compared as the maleate salts. Our original stereochemical assignment for the aminomethyl group as being exo was made purely on the basis of the established thermodynamic stability relationship for endo-exo derivatives of this type.²⁴ This was later supported by chemical evidence involving Huang-Minlon reduction of 29a to the known exo-2-dimethylaminomethylbicyclo[2.2.1]heptane.^{23,45}

Lithium aluminum hydride reduction of 29a or 29b led to a mixture of isomeric aminoalcohols in which the trans isomers predominated. The isomers were fortunately readily separated by fractional distillation and completely differentiated by hydrogen bonding studies in the infrared. Those compounds in which the hydroxyl was cis to the exo-aminomethyl group exhibited only hydrogen bonded OH which was unaffected by dilution. In contrast, the trans isomers exhibited both free and bonded OH and the intensity of the free OH consistently

increased on dilution²⁵ (see experimental section for more complete description and experimental details). In addition, the cis and trans N,N-dimethyl derivatives, ACC 7121-35 and ACC 7121-37 (Table III), were spectrally analyzed using very dilute carbon tetrachloride solution in a high resolution grating spectrophotometer. Under these conditions, the cis isomer exhibited absorption only for bonded OH at 3.05 μ and conversely the trans isomer displayed only OH absorption at 2.77 μ .* In light of these facts, we have assigned the stereochemistry indicated for the aminoalcohols of Table III.

Bicyclic Aminoalcohols

TABLE III



ACC 7121	Stereochemistry of Hydroxyl	R ₁	R ₂	m.p. °C
35	<u>exo</u> (<u>cis</u>)	-CH ₃	-CH ₃	218-219°
37	<u>endo</u> (<u>trans</u>)	-CH ₃	-CH ₃	222-223°
48	<u>endo</u> (<u>trans</u>)	-CH ₂ Ø	-CH ₂ Ø	209-211°
50	<u>exo</u> (<u>cis</u>)	-CH ₂ Ø	-CH ₂ Ø	200-203°
42	<u>endo</u> (<u>trans</u>)	-H	-CH ₂ Ø	254-255°
46	<u>endo</u> (<u>trans</u>)	-H	-H	245°

*We gratefully acknowledge the assistance of Dr. H. Aaron, Army Chemical Center, Edgewood Arsenal, who carried out these analyses.

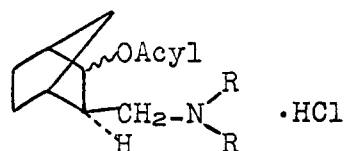
Compounds ACC 7121-42 and ACC 7121-46 obviously resulted from successive reductive debenzoylation of ACC 7121-48.

It is of some interest to note that in comparing the N,N-disubstituted isomers, ACC 7121-35, ACC 7121-37, ACC 7121-48 and ACC 7121-50, in each case the trans isomer was the higher boiling isomer and the free base was a crystalline solid in contrast to the cis isomer where the free base was a liquid.

The tertiary aminoalcohols listed in Table III were converted to the corresponding benzilate esters in those cases where sufficient sample was available. One exception was the acetate, ACC 7121-36, which was prepared early in this study for the purpose of investigating isomer separation possibilities by VPC. These esters are listed in Table IV.

Bicyclic Aminoalcohol Esters

TABLE IV



ACC 7121	Stereo- Chemistry of -OAcyl	Acyl	R	m.p. °C
40	<u>endo</u> (<u>trans</u>)	$\begin{array}{c} \emptyset \\ \\ -C-C-\emptyset \\ \quad \\ O \quad OH \end{array}$	-CH ₃	147-148°
41	<u>exo</u> (<u>cis</u>)	$\begin{array}{c} \emptyset \\ \\ -C-C-\emptyset \\ \quad \\ O \quad OH \end{array}$	-CH ₃	198-200°
47	<u>endo</u> (<u>trans</u>)	$\begin{array}{c} \emptyset \\ \\ -C-C-\emptyset \\ \quad \\ O \quad OH \end{array}$	-CH ₂ ∅	210-211°
53	<u>endo</u> (<u>trans</u>)	$\begin{array}{c} \emptyset \\ \\ -C-C-\emptyset \\ \quad \\ O \quad OH \end{array}$	-H	Free Base 123-124°
36	mixture	$\begin{array}{c} -C-CH_3 \\ \\ O \end{array}$	-CH ₃	169-170°

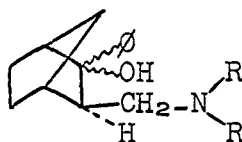
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Two compounds, ACC 7121-41 and ACC 7121-47, were prepared by transesterification of methyl benzilate. Compound ACC 7121-40 was prepared from diphenylchloroacetyl chloride followed by hydrolysis as described earlier in this report for the aminoborneol derivatives. Reductive debenzilation of ACC 7121-47 over Pd/C afforded ACC 7121-53 without difficulty. It was unfortunate that time was not available for the preparation of sufficient quantities of the cis aminoalcohol corresponding to the ACC 7121-47 to allow preparation of the corresponding benzilate ester and subsequent debenzilation to the cis form of ACC 7121-53. The acetate, ACC 7121-36, was prepared using acetic anhydride according to conventional methods.

Treatment of the aminoketones 29a and 29b with phenyl lithium afforded a convenient route to the series of phenylpropanol amines listed in Table IV. These compounds bear a structural relationship to the important neurohormone, norepinephrine, and it was felt that they might be of interest in modifying the action of this important agent.

Phenylpropanol Amines

TABLE V



ACC 7121	Stereo- Chemistry of Hydroxyl	R	Salt	m.p. °C
33	<u>endo</u> (<u>trans</u>)	-CH ₃	Maleate	191-193°
34	<u>exo</u> (<u>cis</u>)	-CH ₃	Maleate	139-141°
58	<u>endo</u> (<u>trans</u>)	-CH ₂ Ø	HCl	133-136°
not submitted due to insuf- ficient sample	<u>exo</u> (<u>cis</u>)	-CH ₂ Ø	HCl	184-186°
56	<u>endo</u> (<u>trans</u>)	-H	HCl	229-230°

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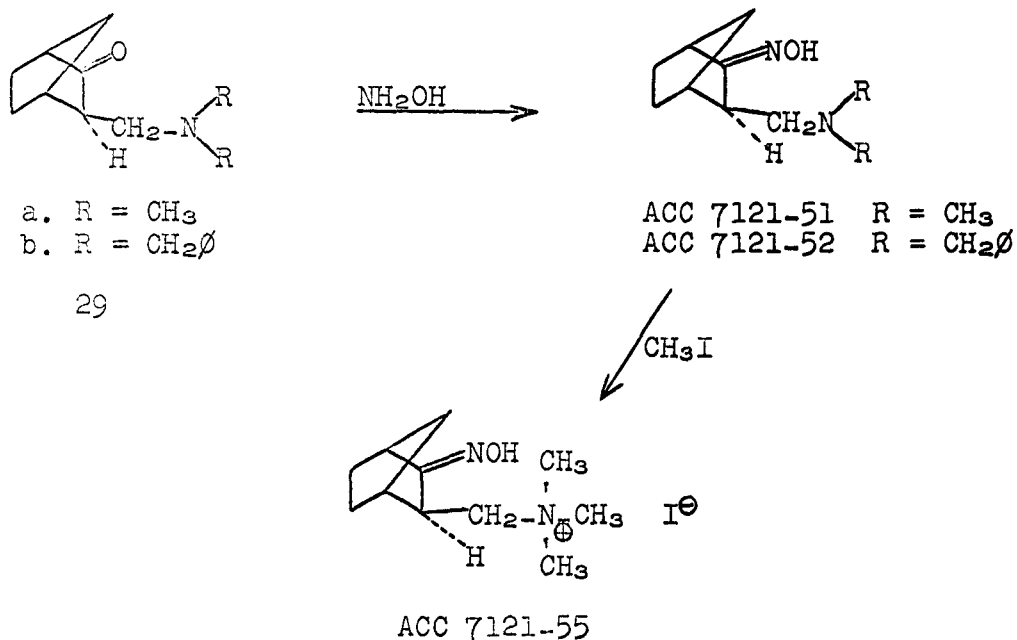
The isomeric aminoalcohols from 29a were readily separated by selective crystallization of the trans isomer, ACC 7121-33, from Skelly B. The cis isomer was recovered from the mother liquors and purified as the maleate salt.

In the case where $R = CH_2\phi$, the major product was the trans isomer, ACC 7121-58, which was separated and purified as the hydrochloride salt. The cis isomer was isolated only in amounts sufficient for identification and characterization.

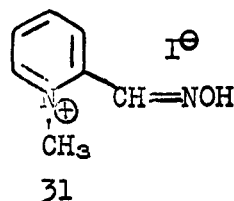
Classical hydrogen bonding studies, along the lines described previously, demonstrated the difference in the isomers and served to establish their configuration. In each case, the assignments are unambiguous and the details are given in the experimental section.

Reductive debenzoylation of ACC 7121-58 afforded in high yield the primary amine ACC 7121-56.

Treatment of 29a and 29b with hydroxylamine afforded the corresponding ketoximes, ACC 7121-51 and ACC 7121-52. Conversion of ACC 7121-51

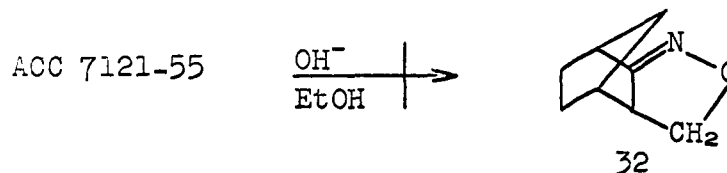


to the methiodide salt afforded ACC 7121-55 which by virtue of its being a quaternary salt of an amino oxime is related to the well-known muscle relaxant and nerve gas (cholinesterase inhibitor type) antidote 2-PAM,²⁸ 31.

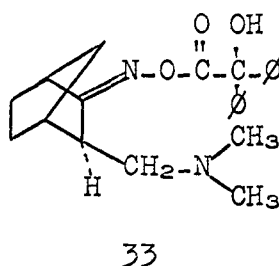


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Attempts to cause the elimination of the trimethylammonium group and cyclization of ACC 7121-55 to the isoxazoline, 32, by treatment with concentrated ethanolic sodium hydroxide solution according to the procedure of Z. Kyi and W. Wilson²⁷ were unsuccessful.

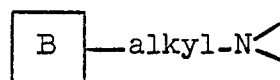


Attempts to prepare O-acyl derivatives of ACC 7121-51, such as 33, were also unsuccessful.



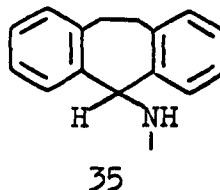
Dibenzo[a,d]cycloheptene Derivatives

Most potent anticholinergic and antihistaminic agents fit a rather general structural pattern exemplified by figure 34, in which B



represents a large bulky grouping, alkyl is an alkyl chain that is attached to B through an ester, ether, amine, or carbon-carbon bond, and N< is normally a tertiary amino group. In the case of the quinuclidyl ester, 1, of this report, B represents the benzylic acid moiety and we felt that a worth-while variation to investigate would involve changing B in such a manner that the basic functional features of B were altered as well as the bonding link to the alkyl chain.

A utility claim in a U. S. Patent²⁸ which described N,N-dialkylamino-alkyl derivatives of 10,11-dihydro-5H-dibenzo[a,d]cycloheptene-5-amine, 35, to be psychomimetic agents encouraged us to utilize the dibenzo-

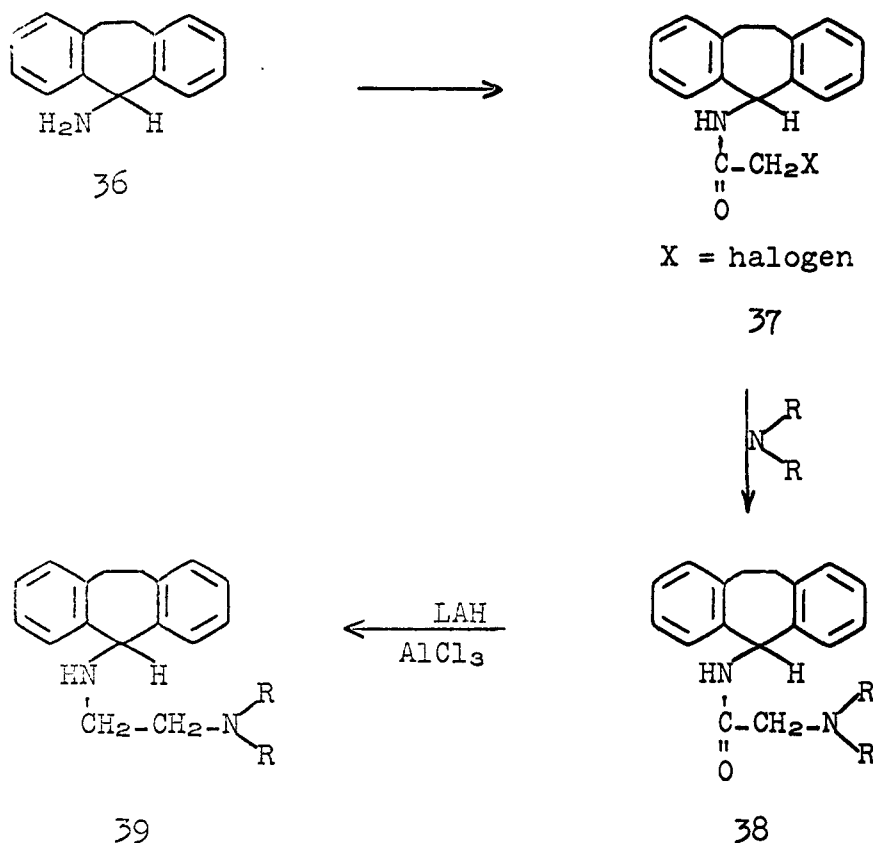


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-[a,d]cycloheptene moiety as the desirable B variant. Compounds in which the attachment of the aminoalkyl chain to the basic ring system is through a carbon-carbon bond are well documented in the literature as psychopharmacologic agents.²⁹

Compounds of type 35 are listed in Table VI and were prepared by two general routes. The procedure as described by Bernstein and Losce²⁸ involved the chloroalkyl acylation of 5-aminodibenzo-

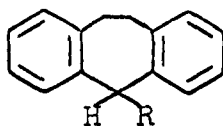
[a,d]cycloheptene, 36, treatment of 37 with dialkylamine and reduction of the acylamine, 38, thus produced with lithium aluminum hydride using aluminum chloride as a catalyst. We found this to be



a workable procedure for the preparation of the compound where R = methyl, ACC 7121-23. However, when R was cyclized into a piperazine ring so that the terminal basic amino group was 4-methyl-1-piperazinyl, ACC 7121-49, three attempts to cause the lithium aluminum hydride reduction to occur were unsuccessful.

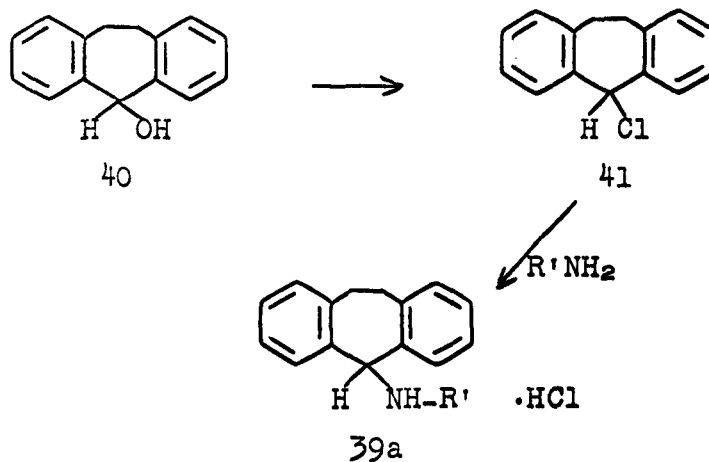
5-Amino Dibenzocycloheptene Derivatives

TABLE VI



ACC 7121	R	Salt	m.p. °C
23	$(\text{CH}_3)_2\text{N}-(\text{CH}_2)_2-\text{N}-\overset{\text{H}}{\underset{ }{\text{C}}}$	HCl	185-187°
28	$(\text{CH}_3)_2\text{N}-\text{CH}_2-\overset{\text{O}}{\underset{\text{H}}{\text{C}}}-\overset{\text{H}}{\underset{ }{\text{N}}}-$	HCl	208°
31	$\text{C}_6\text{H}_{11}\text{N}-(\text{CH}_2)_2-\overset{\text{H}}{\underset{ }{\text{N}}}-$	HCl	208-209°
49	$\text{CH}_3-\text{N}-\text{C}_6\text{H}_{11}\text{N}-\overset{\text{O}}{\underset{\text{H}}{\text{C}}}-\overset{\text{H}}{\underset{ }{\text{N}}}-$		128-130°
54	$\text{HO}-(\text{CH}_2)_2-\overset{\text{CH}_3}{\underset{ }{\text{N}}}-$		b.p., 170.5° (0.4 mm.)
—	$\text{HOCH}_2\text{CH}_2-\text{N}-\text{C}_6\text{H}_{11}\text{N}-$		b.p., 95-97° (0.02 mm.)

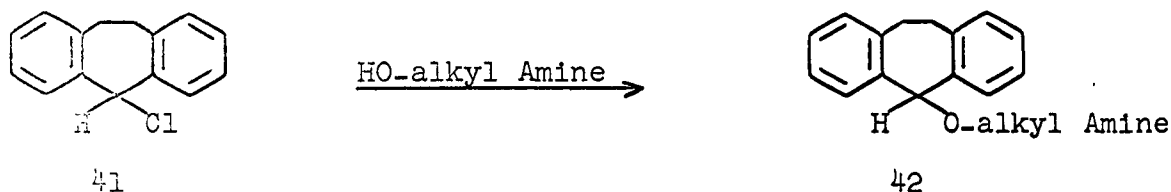
A second synthetic approach to these compounds involved treatment of the alcohol, 40, with hydrochloric acid to yield the chloro compound,^{30,31} 41, and displacement of the chloro group with an amine to yield 39a.



This procedure was used for the preparation of ACC 7121-31, ACC 7121-54 and the hydroxyethylpiperazino base for which no ACC number is assigned. Difficulty was encountered in preparing salts of this latter compound and, therefore, when it was described in the literature³² investigation ceased.

With regard to ACC 7121-54, it is of some interest to note that this hydroxyalkylamine is the reaction product when a large excess, (5 moles amine to 1 mole chloro compound) of amine is employed. When the reagents are in equal concentration, the ether, ACC 7121-57, (Table VII) is the only product isolated.

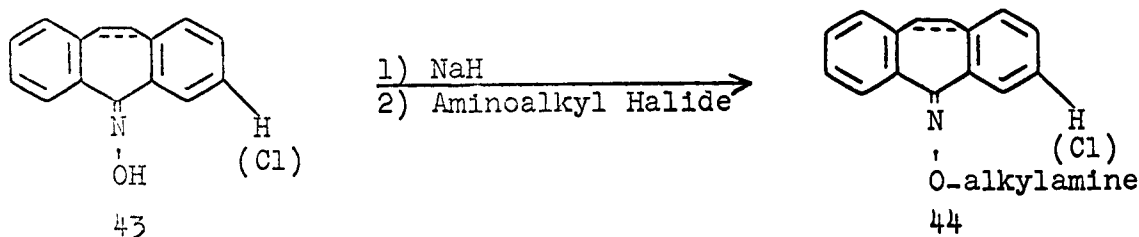
With one exception, ACC 7121-21, the ethers, 42, of Table VII were prepared by treating the 5-chloro derivative, 41, with the appropriate basic aminoalcohol following the procedure described by



van der Stelt.³¹

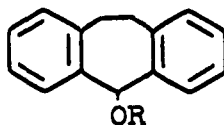
ACC 7121-21 was conveniently prepared by converting the alcohol, 40, into the alcoholate anion with sodium hydride and allowing this to react with dimethylaminoethyl chloride.

The aminocylated oximes listed in Table VIII represent an extension of the basic investigations involving the dibenzo[a,d]cycloheptene system. The parent oximes, 43, were prepared from the corresponding ketones^{33,34} according to the procedure described by Monro et. al.³⁵ for 10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-one oxime. Amino-alkylation was effected by converting the oxime to the anion with



sodium hydride in toluene and treatment with the appropriate amino-alkyl halide.

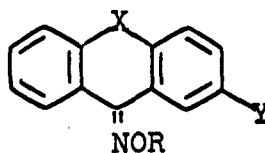
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Dibenzocycloheptene EthersTABLE VII

ACC 7121	R	Salt	m.p. °C
21	$(\text{CH}_3)_2\text{N}-\text{CH}_2\text{CH}_2-$	Maleate	121-122°
22	$\text{CH}_3\text{N} \begin{array}{c} \diagup \quad \diagdown \\ \text{---} \end{array} \text{NCH}_2\text{CH}_2-$	Maleate	174-175°
26		Fumarate	167-168°
27		Maleate	109-110°
30		Fumarate .H ₂ O	163-164°
38		Free Base	112-113°
57	$-\text{C}_2\text{H}_4\text{NHCH}_3$	Maleate	144-146°

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O-Substituted OximesTABLE VIII

ACC 7121	X	Y	R	Salt	m.p. °C
24	-CH ₂ CH ₂ -	H	-C ₂ H ₄ N(CH ₃) ₂	Fumarate	140-142°
29	-CH ₂ CH ₂ -	H	$\begin{array}{c} \text{O} \\ \parallel \\ -\text{C}-\text{OC}_2\text{H}_5 \end{array}$		112-113°
32	-CH ₂ CH ₂ -	H	$\begin{array}{c} \text{CH}_2\phi \\ \\ -\text{C}_2\text{H}_4\text{N}- \\ \\ \text{CH}_3 \end{array}$	Fumarate	149-150°
43	-CH ₂ CH ₂ -	H	-C ₂ H ₄ N  NCH ₃	Maleate	174-175°
59	-CH ₂ CH ₂ -	H	-C ₃ H ₈ N(CH ₃) ₂	Maleate	124-126°
25	-CH=CH-	H	-C ₂ H ₄ N(CH ₃) ₂	Fumarate	159-160°
39	-CH ₂ CH ₂ -	Cl	-H		197-200°
44	-CH ₂ CH ₂ -	Cl	-C ₂ H ₄ N(CH ₃) ₂	Fumarate	143-144°
45	-CH ₂ CH ₂ -	Cl	-C ₂ H ₄ N  NCH ₃	Fumarate	195-196°

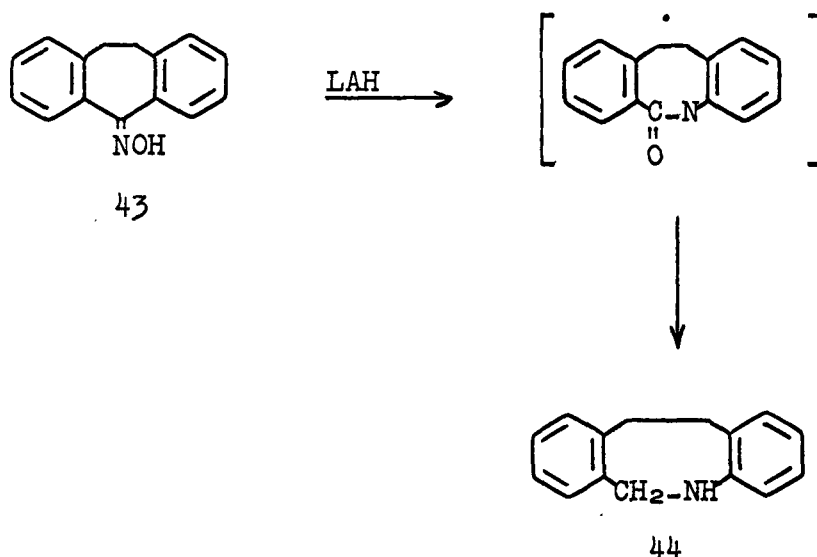
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The O-carboethoxy derivative, ACC 7121-29, was prepared by treatment of the oxime with ethylchloroformate and triethylamine in benzene.

The importance of metabolic demethylation in the formation of in vivo biologically active metabolites has been well documented.^{36, 37} The desmethyl derivative of ACC 7121-24 was judged to be of considerable importance. To date, all synthetic approaches to this compound have failed. These include selective removal of the N-benzyl blocking group in ACC 7121-32, as well as more basic exploratory synthetic approaches.

One aspect of our program concerning the chemistry of the oximes,⁴³ involved using these compounds as intermediates to the 5-aminodibenzo-[a,d]cycloheptenes, 36. Monro³⁵ had observed that lithium aluminum hydride reduction of 10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-one oxime did not take the anticipated course. We investigated this reaction and obtained in high yield a solid base which was different than the 5-amino derivative, 36.



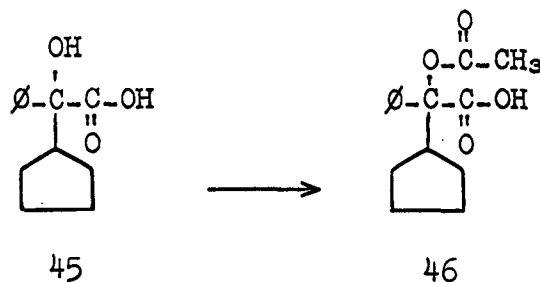
Since it is known that lithium aluminum hydride can perform as a Lewis acid and that Beckman rearrangements have been reported for compounds of this type,³⁸ we felt that the amine 44 was a reasonable structural projection for the product obtained. The amine 44 was synthesized following the procedure of Monro³⁵ and determined to be identical to the lithium aluminum hydride reduction product as evidenced by mixed melting point and infrared spectral comparison.

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Miscellaneous Projects

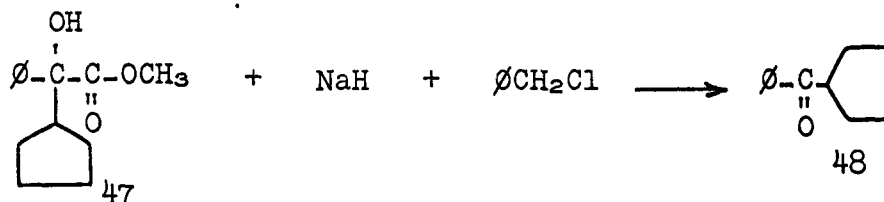
The most important project relating to this program, but not dealing with the synthesis of new compounds, involved exploratory experimentation on the resolution of phenylcyclopentylglycolic acid.

Initially, the experiments were concerned with attempts to modify the molecule by use of an appropriate blocking group on the alcohol hydroxyl. It was hoped that the acid derivative thus obtained would be more readily separated into its optical forms using an appropriate resolving amine.



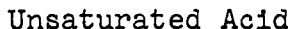
Acetylation was accomplished using acetic anhydride, but the acetate, 46, would not form an ether insoluble salt with optically active α -(α -naphthyl)ethylamine.

Attempts to introduce the benzyl grouping using benzyl chloride and sodium hydride on the methyl ester 47 resulted in the formation of a ketone as a minor reaction product. VPC and infrared spectral



analysis of the crude product obtained suggested that phenylcyclopentyl ketone, 48, might be present. An authentic sample of 48 was prepared for these studies. None of the desired O-benzyl derivatives could be isolated.

An alternate synthetic approach involved the preparation of the chloro acid chloride, 49, treatment with benzyl alcohol and base catalyzed hydrolysis of the resulting ether ester 50. However, only uncharacterized unsaturated acids were obtained.



ethyl bromide afforded the desired aminoalcohol 54. Transesterifying with methylphenylcyclopentyl glycolate and thermal ring expansion yielded the piperidyl ester 56. This compound, on fractional crystallization of the hydrochloride salt from acetonitrile, afforded a sharp melting isomer, m.p. 231-232°C. This material on hydrolysis afforded a sample of optically active acid, α_D^{25} DMF (-5.6°). This research was not pursued beyond this stage but in the opinion of the authors, represents a valid approach if it is desired to obtain both isomers of this acid in pure form.

m-Benzoyloxybenzoyl Chloride

This compound was prepared from m-hydroxybenzoic acid following the procedure of Cavallito and Buck.⁵ The intermediate, m-benzyloxybenzoic acid, had a m.p. of 123-126°C and was obtained from the ester in 90% yield. The crude acid chloride isolated from the reaction mixture was obtained as a yellow-green oil and was used without further purification.

Anal. Calcd. for $C_{14}H_{11}ClO_2$: Cl, 14.38. Found: Cl, 12.64.

3-Quinuclidyl m-Benzoyloxybenzoate Hydrochloride, ACC 7121-11

A solution of 48.5 g. (0.197 mole) m-benzyloxybenzoyl chloride in 200 ml. chloroform was added dropwise with stirring to a solution of 25.0 g. (0.197 mole) 3-quinuclidinol in 100 ml. chloroform and the resulting mixture was stirred at reflux for 4.5 hours. The solids were separated by filtration from the hot solution and the filtrates were evaporated under reduced pressure. The oily residues, 64.1 g. (84.5%), crystallized when treated with anhydrous ether yielding 34.4 g. (46.7%) of product, m.p. 169-172°C. Ten grams of this solid was dissolved in isopropanol, treated with Darco, filtered and cooled. The solids which separated were collected by filtration, and recrystallized a second time from isopropanol, yielding 7.23 g., m.p. 186-188°C.

Anal. Calcd. for $C_{21}H_{24}ClNO_3$: C, 67.46; H, 6.47; N, 3.75; Cl, 9.48. Found: C, 67.3; H, 6.7; N, 3.71; Cl, 9.51.

3-Quinuclidyl-p-benzyloxybenzoate Hydrochloride, ACC 7121-9

This compound has been prepared by two methods.

A. A mixture of 6.85 g. (0.05 mole) 3-quinuclidinol and 2.40 g. (0.05 mole) 50% sodium hydride and 100 ml. dry toluene was stirred at reflux for one hour, cooled slightly and a solution consisting of 12.30 g. (0.05 mole) 4-benzyloxybenzoyl chloride⁵ in 100 ml. dry toluene was added and the mixture stirred at reflux for two hours and cooled. The inorganic solids were removed by filtration. The filtrates were evaporated under reduced pressure and the residues solidified yielding 17.6 g. (104.0%). The residues were dissolved in ether, filtered through a Celite bed and acidified with anhydrous hydrogen chloride. Solids formed rapidly and were collected by filtration and recrystallized from isopropanol yielding 10.58 g. (28.4%) m.p. 236°C.

Anal. Calcd. for $C_{21}H_{24}ClNO_3$: C, 67.46; H, 6.47; N, 3.75; Cl, 9.48. Found: C, 67.05; H, 7.0; N, 3.78; Cl, 9.54.

3-Quinuclidyl-p-benzyloxybenzoate Hydrochloride, ACC 7121-9

B. This procedure was essentially identical to that described for ACC 7121-11. The pure product obtained in 26% yield was identical to that obtained from procedure A.

3-Quinuclidyl-o-hydroxybenzoate Hydrochloride, ACC 7121-5

A mixture of 6.85 g. (0.05 mole) 3-quinuclidinol, 2.4 g. (0.05 mole) 50% sodium hydride and 100 ml. dry toluene was stirred and refluxed for one hour and cooled slightly, 7.8 g. (0.05 mole) o-hydroxybenzoyl chloride⁴ in 25 ml. toluene was added dropwise. The mixture was stirred at reflux for two hours, cooled and the inorganic salts removed by filtration. The filtrates were evaporated to dryness under reduced pressure (11.5 g.), and dissolved in dry ethyl ether. Small amounts of solids were filtered off and the filtrates acidified with anhydrous hydrogen chloride. The white solids which formed were collected by filtration and recrystallized twice from hot ethanol yielding 5.27 g. (37.4%) m.p. 266-267°C.

Anal. Calcd. for $C_{14}H_{18}ClNO_3$: C, 59.26; H, 6.39; O, 16.91.
Found: C, 59.1; H, 6.4; O, 16.9.

3-Quinuclidyl-m-hydroxybenzoate Hydrochloride, ACC 7121-6

A mixture of 23.0 g. (0.06 mole) 3-quinuclidyl-m-benzyloxybenzoate hydrochloride, 250 ml. methanol, 25 ml. water was treated under 60 psi hydrogen at 40°C with 1.5 g. 10% palladium on carbon until the uptake of hydrogen ceased. The catalyst was removed by filtration and the filtrates were evaporated under reduced pressure. The tan gum, 17.6 g., (100.5%) was covered with anhydrous ether and the solids which formed were recrystallized from ethanol yielding 6.8 g. (44.8%) m.p. 245-247°C.

Anal. Calcd. for $C_{14}H_{18}ClNO_3$: C, 59.26; H, 6.39; N, 4.93; Cl, 12.49.
Found: C, 59.3; H, 6.4; N, 4.97; Cl, 12.49.

3-Quinuclidyl-p-hydroxybenzoate Hydrochloride, ACC 7121-7

This was prepared from 6.75 g. (0.018 mole) of ACC 7121-9 according to the procedure described for ACC 7121-6 yielding 2.9 g. (55.8%) m.p. 259-261°C.

Anal. Calcd. for $C_{14}H_{18}ClNO_3$: C, 59.26; H, 6.39; O, 16.91.
Found: C, 59.2; H, 6.5; O, 17.2.

3-Quinuclidyl-3,4,5-trimethoxybenzoate Hydrochloride, ACC 7121-12

3,4,5-Trimethoxybenzoyl chloride³⁹ was treated with 3-quinuclidinol essentially according to the procedure described for ACC 7121-11. The pure product was obtained in 22% yield, m.p. 214-216°C.

Anal. Calcd. for $C_{17}H_{24}ClNO_5$: C, 57.06; H, 6.76; N, 3.91; Cl, 9.91.
Found: C, 57.0; H, 7.0; N, 3.90; Cl, 9.93.

3-Quinuclidyl-p-chlorophenoxyacetate Hydrochloride, ACC 7121-10

p-Chlorophenoxyacetyl chloride⁴⁰ was converted to the quinuclidyl ester according to the procedure described for ACC 7121-11. The pure product was obtained in 51% yield, m.p. 199-201°C.

Anal. Calcd. for $C_{15}H_{19}Cl_2NO_3$: C, 54.23; H, 5.77; N, 4.22; Cl, 21.35.
Found: C, 54.0; H, 6.2; N, 4.22; Cl, 21.93.

3-Quinuclidyl Phenylacetate Hydrochloride, ACC 7121-18

A mixture of 24.6 g. (0.15 mole) ethyl phenylacetate,⁴¹ 19.0 g. (0.15 mole) 3-quinuclidinol and 4.36 g. aluminum isopropoxide was stirred under 80 mm. pressure at 120°C for one hour and at 150°C for two additional hours. Fifty ml. of saturated sodium chloride solution was added to the reaction mixture. White solids formed and were removed by filtration. The filtrates were thoroughly extracted with ethyl ether and back extracted with 6N hydrochloric acid. The ether layers were discarded and the aqueous extract saturated with sodium bicarbonate. The pH was adjusted to 10 with potassium carbonate and the solution extracted several times with ethyl ether. The organic phases were dried over anhydrous potassium carbonate, filtered and acidified carefully to pH 5 with ethereal hydrogen chloride. White solids formed rapidly and were collected by filtration yielding 27.4 g. of product, m.p. 162-164°C. The solids were recrystallized from hot acetonitrile (100 ml.), treated with Darco, filtered and cooled. The solids were collected by filtration yielding 12.5 g. (29.6%), m.p. 180-181°C.

Anal. Calcd. for $C_{15}H_{20}ClNO_2$: C, 63.92; H, 7.15; N, 4.97; Cl, 12.58.
Found: C, 63.92; H, 7.11; N, 5.05; Cl, 12.70.

3-Quinuclidyl Lactate, ACC 7121-1

A mixture of 17.7 g. (0.15 mole) redistilled ethyl lactate, 19.2 g. (0.15 mole) 3-quinuclidinol, 150 ml. dry toluene and 3.0 g. aluminum isopropoxide were refluxed with stirring for three hours. The reaction mixture was then heated in an oil bath at 120°C under 80 mm. pressure

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for one hour. The oily residues were extracted from a saturated sodium chloride solution with ether. The ether extracts were acidified with ethereal hydrogen chloride and an oil separated. The residue, after decanting the ether, was dissolved in 30 ml. hot isopropanol and diluted with ether to the cloud point. Unreacted 3-quinuclidinol precipitated as the hydrochloride salt and was removed by filtration. The filtrates were evaporated under reduced pressure and dissolved in a mixture of 25 ml. ethyl acetate and 25 ml. acetonitrile affording an additional quantity of 3-quinuclidinol hydrochloride which was removed by filtration. The filtrates were then evaporated under reduced pressure and the residue converted to the free base. The base was distilled through a short still head under reduced pressure yielding 2.8 g. of product, b.p. 95°C (0.02 mm.). The distillate solidified on standing, m.p. $73-76^{\circ}\text{C}$.

Anal. Calcd. for $\text{C}_{10}\text{H}_{17}\text{NO}_3$: C, 60.29; H, 8.60. Found: C, 60.47; H, 8.61.

Methyl Atrolactate

A mixture of 39.8 g. (0.24 mole) atrolactic acid,⁴² 240 ml. methanol and 12 ml. concentrated sulfuric acid was stirred at reflux for 12 hours, cooled, and diluted with an equal volume of water. This solution was saturated with a mixture of sodium bicarbonate and sodium chloride and extracted with three 250 ml. portions of ethyl ether. The organic phases were dried over anhydrous magnesium sulfate, filtered and the ether distilled off through a 10" column. The residues were fractionated through a 5" column under reduced pressure yielding 36.53 g. (84.5%), b.p. $119-120^{\circ}\text{C}$ (10 mm.).

Anal. Calcd. for $\text{C}_{10}\text{H}_{12}\text{O}_3$: Sap. Eq. 180.19. Found: Sap. Eq. 181.9.

3-Quinuclidyl Atrolactate Hydrochloride, ACC 7121-4

A mixture consisting of 18.5 g. (0.1 mole) methyl atrolactate, 12.7 g. (0.1 mole) 3-quinuclidinol, 2.0 g. aluminum isopropoxide and 100 ml. dry toluene was stirred at reflux for three hours; and then heated in an oil bath at 120°C under 80 mm. pressure for one hour. The cooled reaction mixture was dissolved in 50 ml. water and extracted with ethyl ether. The ether extracts were dried over anhydrous potassium carbonate, filtered, and acidified with anhydrous hydrogen chloride. The ether was decanted from the yellow oils which formed, the oil was dissolved in 20 ml. warm isopropanol, diluted to the cloud point with ether, and allowed to crystallize. The solids were collected by filtration, combined with previously prepared material (6.15 g. total), dissolved in 580 ml. hot acetonitrile, treated with Darco, filtered and allowed to cool. The resulting solids were collected by filtration and dried yielding 2.3 g., m.p. $244-245^{\circ}\text{C}$.

Anal. Calcd. for $\text{C}_{16}\text{H}_{22}\text{ClNO}_3$: C, 61.63; H, 7.11. Found: C, 61.4; H, 7.2.

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Methyl-2,2-diphenyl Hydracrylate

To a 23.5 g. (0.36 mole) sample of freshly cleaned and prepared zinc dust (washed consecutively with 2% hydrochloric acid, water, absolute ethanol, acetone, ethyl ether and rigorously dried) was added a mixture of 54.7 g. (0.3 mole) of benzophenone, 45.9 g. (0.3 mole) methyl- α -bromoacetate and 80 ml. of dry benzene in a dropwise fashion with stirring. When the addition was one fourth complete, the mixture was warmed to reflux on a steam bath. When the addition was one third complete, the reaction became exceedingly exothermic and the heat source was removed until the vigorous reaction had subsided. The addition was then completed while maintaining reflux by the addition of heat. Periodically during the addition the reaction became exothermic at which time the heat source was removed. When the addition was complete, an additional 20 ml. dry benzene was added to the heavy pale gray slurry and the mixture was stirred at reflux for one hour. After cooling to room temperature, the mixture was hydrolyzed by the addition of 150 ml. of 20% ice cold sulfuric acid solution. An additional 150 ml. of benzene was added to dissolve the partially precipitated product and the mixture was transferred to a separatory funnel and the layers separated. The aqueous phase was washed twice with 50 ml. portions of benzene. The combined benzene extracts were washed twice with 30 ml. portions of 20% sulfuric acid, with 25 ml. of 10% sodium carbonate solution and finally with 25 ml. portions of water. After drying over anhydrous magnesium sulfate overnight, the benzene was removed under reduced pressure leaving a pale yellow solid, 65.5 g. (85.3%), m.p. 100-101°C.

Anal. Calcd. for $C_{16}H_{16}O_3$: C, 74.98; H, 6.30; Sap. Eq., 256.29.
Found: C, 75.15; H, 6.22; Sap. Eq., 265.4.

 β,β -Diphenyl- β -hydroxypropionic Acid

A mixture of 25.6 g. (1.0 mole) methyl-2,2,-diphenylhydracrylate, 11.2 g. (0.2 mole) potassium hydroxide and 250 ml. methanol and 1 ml. water was stirred at reflux for 4 hours. The solution was evaporated to dryness, the residues dissolved in 300 ml. water and acidified with 25 ml. concentrated hydrochloric acid. The white solids which formed were collected by filtration and dried yielding 20.5 g. (84.5%), m.p. 220°C.

Anal. Calcd. for $C_{15}H_{14}O_3$: C, 74.35; H, 5.32; N.E. 242.2.
Found: C, 74.40; H, 5.74; N.E., 255.3.

3-Quinuclidyl β,β -Diphenyl- β -hydroxypropionate Hydrochloride, ACC 7121-8

To a suspension of 5.8 g. (0.15 mole) sodium amide in 300 ml. liquid ammonia was added a solution of 12.7 g. (0.075 mole) 3-quinuclidyl acetate⁴³ in 50 ml. anhydrous ether, followed immediately by a solution of 13.7 g. (0.075 mole) benzophenone in 50 ml. of anhydrous ether. The mixture was stirred for fifteen minutes and then quenched by the addition of 16 g. (0.300 mole) solid ammonium chloride. The ammonia was evaporated, the residue dissolved in 50 ml. water, extracted into ether, and the extracts were dried over magnesium sulfate. The dry ether

solution was acidified with ethereal hydrochloric acid. The gummy solid was isolated by decantation, triturated in hot ethyl acetate, and collected by filtration yielding 7.7 g. (26.5%), m.p. 218-219°C. Recrystallization from ethanol afforded 6.45 g. of product, m.p. 243°C.

Anal. Calcd. for $C_{22}H_{26}ClNO_3$: C, 68.12; H, 6.75. Found: C, 68.18; H, 6.66.

3-Quinuclidyl α -Bromophenylacetate Hydrobromide, ACC 7121-13

A solution of 12.7 g. (0.1 mole) 3-quinuclidinol in 100 ml. chloroform was added dropwise with stirring to a solution of 27.8 g. (0.1 mole) α -bromophenylacetyl bromide⁴⁴ in 100 ml. chloroform and the resulting mixture stirred at reflux for 3.5 hours. The solids which formed were removed by filtration and the filtrates evaporated under reduced pressure. The residues were dissolved in acetone and the solids which formed rapidly were collected by filtration yielding 9.9 g. (25%), m.p. 183-185°C.

Anal. Calcd. for $C_{15}H_{19}Br_2NO$: C, 44.46; H, 4.73; N, 3.46; Br, 39.45. Found: C, 44.7; H, 4.9; N, 3.52; Br, 39.37.

3-Quinuclidyl Acetoacetate Hydrochloride, ACC 7121-14

A mixture consisting of 12.7 g. (0.1 mole) of 3-hydroxyquinuclidine and 65.1 g. (0.5 mole) of ethyl acetoacetate was heated on a steam bath for three hours. The mixture was then heated under vacuum to remove ethanol and excess ethyl acetoacetate. The residue (20.5 g.) was dissolved in 100 ml. ether and upon acidification with ethereal hydrochloric acid a gummy solid formed. The ether was removed by decantation and the residue was dissolved in 100 ml. hot ethyl acetate. Cooling afforded a solid which was collected by filtration yielding 17.4 g. (72.0%), m.p. 177-178°C.

Anal. Calcd. for $C_{11}H_{18}ClNO_3$: C, 53.34; H, 7.33. Found: C, 53.52; H, 7.51.

3-Quinuclidyl Benzoylacetate Hydrochloride, ACC 7121-15

A mixture consisting of 12.7 g. (0.1 mole) 3-hydroxyquinuclidine and 77 g. (0.4 mole) ethyl benzoylacetate was heated on a steam bath for three hours. The mixture was heated under vacuum to remove ethanol and excess ethyl benzoylacetate.

The residue (34 g.) was dissolved in 200 ml. ether and acidified with ethereal hydrochloric acid. The ether was removed by decantation and the residue was dissolved in 175 ml. hot ethyl acetate. Cooling afforded a solid which was collected by filtration yielding 6.05 g., m.p. 158-159°C.

Anal. Calcd. for $C_{18}H_{20}ClNO_3$: C, 62.03; H, 6.50; Found: C, 62.22; H, 6.70.

3-Quinuclidyl β -Hydroxybutyrate Hydrochloride, ACC 7121-16

A mixture consisting of 6.4 g. (0.03 mole) 3-quinuclidyl acetoacetate hydrochloride, 0.3 g. platinum oxide and 100 ml. ethanol was placed in a Parr hydrogenator and heated to 50°C under 60 psi hydrogen for two hours. The catalyst was filtered off through Celite, and the filtrate evaporated to dryness. The residue, 6.05 g. (m.p. 150-153°C), was recrystallized from isopropanol yielding 3.6 g., m.p. 155-156°C.

Anal. Calcd. for $C_{11}H_{20}ClNO_3$: C, 52.89; H, 8.07. Found: C, 52.59; H, 7.82.

2-Quinuclidylmethanol¹⁰

To a suspension of 2.6 g. (0.067 mole) lithium aluminum hydride in 50 ml. tetrahydrofuran was added 12.3 g. (0.067 mole) ethyl-2-quinuclidyl carboxylate⁹ in 50 ml. tetrahydrofuran and the mixture stirred at reflux for three hours. The excess hydride was decomposed by the addition of 3 ml. water and the complex was decomposed with 17 ml. 40% potassium hydroxide. The inorganic salts were removed by filtration and filtrates dried over anhydrous potassium carbonate. The product was distilled under reduced pressure yielding 7.2 g. (76.5%), b.p. 120-121°C (mm.), of product which slowly crystallized.

Anal. Calcd. for $C_8H_{15}NO$: C, 68.04; H, 10.71; N, 9.92. Found: C, 66.25; H, 10.97; N, 9.75.

2-Quinuclidylmethanol Hydrochloride

An ethereal solution of 2.0 g. above base was acidified with anhydrous hydrogen chloride and the solids collected by filtration. Recrystallization from acetonitrile yielded 1.75 g. (70.0%), m.p. 321-322°C, of the desired salt.

Anal. Calcd. for $C_8H_{15}ClNO$: C, 54.07; H, 9.13; N, 7.88; Cl, 19.95. Found: C, 53.74; H, 9.27; N, 7.75; Cl, 20.09.

2-Quinuclidylmethyl Benzilate Hydrochloride, ACC 7121-17

A mixture of 5.0 g. (0.0355 mole) 2-quinuclidylmethanol, 8.6 g. (0.0355 mole) methyl benzilate, 250 ml. n-heptane and a freshly prepared solution of 0.1 g. sodium in 5 ml. methanol was stirred at reflux as 7.8 ml. methanol distilled off and was collected in a Dean-Stark separator. The reaction mixture was filtered warm and the filter bed washed with chloroform. The organic filtrates were washed twice with 50 ml. portions of water and dried briefly over anhydrous potassium carbonate. The solvent was evaporated under reduced pressure. The 7.2 g. yellow solids remaining were dissolved in ethanol and acidified with anhydrous hydrogen chloride. The solids which precipitated were collected by filtration and recrystallized from acetonitrile yielding 5.0 g. (36.5%) of product, m.p. 262°C.

Anal. Calcd. for $C_{22}H_{26}ClNO_3$: C, 68.12; H, 6.75; N, 3.61; Cl, 9.14.
Found: C, 68.24; H, 6.74; N, 3.61; Cl, 9.27.

d,1- α -Isonitrosocamphor

To a mixture of 54.0 g. (1.0 mole) sodium methoxide in 100 ml. ethyl ether at $-10^{\circ}C$, a solution of 152.2 g. (1.0 mole) d,1-camphor, 117.2 g. (1.0 mole) isoamyl nitrite (freshly distilled) and 250 ml. ethyl ether was added with stirring. The resulting mixture was stirred at $0^{\circ}C$ for one hour, then at $25^{\circ}C$ overnight. The mixture was poured into 300 g. ice-water and the organic layer was separated. The aqueous extract was washed twice with 100 ml. ether and neutralized with 60 g. (1.0 mole) glacial acetic acid. The oily portions were extracted into ether and the dried extracts were evaporated under reduced pressure. The residues were diluted with 400 ml. Skelly B and the solids collected by filtration yielding 63.0 g. (34.8%) of product, m.p. $108-110^{\circ}C$.

d,1- α -Aminocamphor¹¹

To a stirred mixture of 120 ml. 30% sodium hydroxide, 120 ml. water and 27.0 g. (0.15 mole) d,1- α -isonitrosocamphor was added 36.0 g. (0.56 mole) 20 mesh granulated zinc and the resulting mixture was stirred at $20-25^{\circ}C$ for three hours and filtered through Celite. The organic portions were extracted into ethyl ether and dried.

The above prepared d,1- α -aminocamphor was used at once, no product was isolated due to its instability.

d,1- α -Aminoborneol

d,1- α -Isonitrosocamphor (40 g.) was reduced according to the above procedure and the crude aminocamphor thus obtained was used without purification.

To a suspension of 25.2 g. (1.10 mole) sodium sand in 100 ml. anhydrous ethyl ether was added the above filtered ether solution of d,1- α -aminocamphor followed by the dropwise addition of 300 ml. water at such a rate as to cause brisk reflux. After all of the sodium had reacted, the mixture was stirred for 1.25 hours and the layers separated. The aqueous layer was washed twice with 100 ml. ether, the combined ether layers were dried, filtered and acidified with ethereal hydrogen chloride. The white solids which formed were collected by filtration and dried. The solids were dissolved in water, saturated with sodium hydroxide and the organic fraction extracted into ether. The dried ether extracts were filtered and evaporated under reduced pressure yielding 30.81 g. (82.7%) of product. A 5.4 g. sample was further purified by sublimation yielding 5.0 g. of pure product, m.p. $182-183^{\circ}C$.

d,1- α -Aminoborneol Hydrochloride

An ethereal solution of 4.0 g. (0.0236 mole) d,1- α -aminoborneol was acidified with ethereal hydrogen chloride. The solids were collected by filtration and recrystallized from 800 ml. hot ethyl acetate to which a small amount of ethanol was added. Upon cooling, a crystalline solid separated which was collected by filtration. The filtrates were evaporated and more solids collected. The combined solids were slurried in hot acetone and collected by filtration yielding 3.0 g. (62.0%) of product, m.p. 285°C.

Anal. Calcd. for $C_{10}H_{20}ClNO$: C, 58.39; H, 9.80; Cl, 17.23; N, 6.81. Found: C, 58.26; H, 9.63; Cl, 17.43; N, 6.69.

d,1- β -Aminoborneol

d,1- α -Isonitrosocamphor (27.0 g., 0.15 mole) was reduced according to the above described procedure and the crude aminocamphor thus obtained was used without further purification.

To a suspension of 6.0 g. (0.15 mole) lithium aluminum hydride in 100 ml. tetrahydrofuran was added the above prepared ether solution of d,1- α -aminocamphor and the resulting mixture was refluxed for two hours. The excess hydride was decomposed with 5 ml. water and the complex was hydrolyzed with 15 ml. (40%) potassium hydroxide solution. The inorganic salts were removed by filtration and the dried organic filtrates were evaporated under reduced pressure. The resulting residues (23.0 g.) were triturated under Skelly B and collected by filtration yielding 12.0 g. (47.4%) of product, m.p. 170-171°C.

Anal. Calcd. for $C_{10}H_{19}NO$: C, 70.94; H, 11.31; N, 8.37. Found: C, 70.45; H, 11.31; N, 8.48.

d,1- α -N-Methylaminoborneol

A mixture of 25.4 g. (0.15 mole) d,1- α -aminoborneol, 22.3 g. (0.30 mole) ethyl formate and 25 ml. ethanol was refluxed for two hours and the solvents removed under reduced pressure leaving 29.2 g. (99.5%), of residue. The residue was dissolved in 150 ml. tetrahydrofuran and added to a stirred suspension of 11.4 g. (0.30 mole) lithium aluminum hydride in 100 ml. tetrahydrofuran. The resulting reaction mixture was stirred at reflux for four hours. The excess hydride was decomposed with 6 ml. water and the complex was hydrolyzed with 25 ml. (40%) potassium hydroxide and the inorganic salts removed by filtration. The filtrates were dried over anhydrous potassium carbonate and after removing the solvents under reduced pressure, the residue was distilled yielding 22.05 g. (80.5%), b.p. 99-100°C (1.2 mm.).

Anal. Calcd. for $C_{11}H_{21}NO$: N, 7.64. Found: N, 7.53.

d,1- α -N,N-Dimethylaminoborneol.

A mixture of 21.0 g. (0.115 mole) d,1- α -methylaminoborneol and 17.0 g. (0.230 mole) ethyl formate was heated in an autoclave at 100°C for two hours. At the end of this time, the mixture had a pH of 7.5. The solvents were removed under reduced pressure, the residues were dissolved in 100 ml. tetrahydrofuran and added to a suspension of 8.5 g. (0.0224 mole) lithium aluminum hydride in 100 ml. tetrahydrofuran. The mixture was stirred at reflux for four hours. The excess hydride was decomposed with 5 ml. water and the complex destroyed with 16 ml. 40% potassium hydroxide solution. The inorganic salts were removed by filtration and the filtrates dried over anhydrous potassium carbonate. The solvents were removed by distillation and the residues distilled under reduced pressure yielding 17.65 g. (77.7%) of product, b.p. 83-85°C (0.5 mm.) which partially solidified on standing.

Anal. Calcd. for $C_{12}H_{23}NO$: N, 7.10. Found: 7.10.

d,1- α -N,N-Dimethylaminoborneol Hydrochloride

The above base (3.94 g., 0.02 mole) was dissolved in ethyl ether and acidified with ethereal hydrochloric acid. The solids were collected by filtration and purified by recrystallization from acetone yielding 4.45 g. of product, m.p. 268°C. A further crystallization of 2.0 g. from 300 ml. hot acetonitrile yielded 1.1 g. of pure product, m.p. 280°C.

Anal. Calcd. for $C_{12}H_{24}ClNO$: C, 61.65; H, 10.35; N, 5.99.
Found: C, 61.02; H, 10.31; N, 6.40.

d- α -N,N-Dimethylaminoborneol

A mixture consisting of 16.9 g. (0.10 mole) d- α -aminoborneol, 19.7 g. (0.38 mole) (88%) formic acid and 9.5 g. (0.12 mole) (37%) formaldehyde was refluxed for five hours. To the above solution was added 10 ml. concentrated hydrochloric acid and then the mixture was evaporated to dryness under vacuum. The residue was dissolved in 100 ml. water, saturated with sodium hydroxide and the oil was extracted into ether. Extracts were dried over potassium carbonate, and the product was collected by distillation, b.p. 107-109°C (4.5 mm.), reported 259-261°C atmospheric pressure.²⁴ Wt. 12.3 g. (62.5%).

Anal. Calcd. for $C_{12}H_{23}NO$: N, 7.10. Found: N, 7.07.

d,1- β -N-Methylaminoborneol

This compound was prepared by the same procedure as used for d,1- α -N-methylaminoborneol as reported previously in 85% yield, b.p. 96-99°C (2.3 mm.).

d,1- β -N,N-Dimethylaminoborneol

This compound was prepared by the procedure described for d,1- α -N,N-dimethylaminoborneol in 89% yield, b.p. 70-78°C (0.07 mm.).

Anal. Calcd. for $C_{12}H_{23}NO$: N, 7.10. Found: N, 7.06.

1,7,7-Trimethyl-endo-2-benzilyloxy-endo-3-(N,N-dimethylamino)-bicyclo[2.2.1]heptane Hydrochloride, ACC 7121-20

A mixture consisting of 6.71 g. (0.034 mole) of d,1- β -N,N-dimethylaminoborneol and 1.63 g. (0.034 mole) 50% sodium hydride in 150 ml. dry toluene was stirred and refluxed for two hours. The reaction mixture was cooled to 35°C and a solution of 9.06 g. (0.034 mole) α -chlorodiphenylacetyl chloride in 50 ml. dry toluene was added all at once, and the resulting mixture was stirred at reflux for three hours. After cooling 60 ml. (5%) sodium bicarbonate solution was added with stirring, the toluene layer separated and washed with an additional 25 ml. of sodium bicarbonate solution. After drying over anhydrous potassium carbonate, the solution was filtered and evaporated under reduced pressure leaving 14.3 g. (103.0%) of an oily residue which was suspended in hot water and acidified with 6N aqueous hydrochloric acid. The aqueous acid was decanted from the gummy residues which crystallized when they were covered with ethyl acetate. The solids were collected by filtration yielding 5.05 g. (33.3%) of product, m.p. 281-282°C. The solids were recrystallized from 75 ml. hot acetonitrile yielding 2.6 g. (16.1%) of pure product, m.p. 284-285°C.

Anal. Calcd. for $C_{28}H_{34}ClNO_3$: C, 70.33; H, 7.90; N, 3.15; O, 10.81. Found: C, 70.7; H, 8.1; N, 3.17; O, 11.39.

1,7,7-Trimethyl-2-exo-hydroxy-3-exo-aminobicyclo[2.2.1]heptane

A solution of 36.0 g. (0.20 mole) d,1- α -isonitrosocamphor in 150 ml. tetrahydrofuran was added dropwise to a stirred suspension of 20.0 g. (0.50 mole) lithium aluminum hydride in 200 ml. tetrahydrofuran and the resulting mixture was stirred at reflux for four hours. The excess hydride was decomposed with 10 ml. water and the complex was hydrolyzed with 25 ml. 40% potassium hydroxide. The inorganic salts were removed by filtration and the dried filtrates were evaporated under reduced pressure. The residues were solid yielding 31.2 g. (92.5%) of product, m.p. 191-195°C. The product was purified by sublimation yielding 29.15 g. (86.0%) of product. The base was converted to the hydrochloride by treatment with anhydrous hydrochloric acid in ether. The product, obtained in 57% yield, had a m.p. of 292-294°C.

Anal. Calcd. for $C_{10}H_{20}ClNO$: C, 58.39; H, 9.80; N, 6.81; Cl, 17.23. Found: C, 57.80; H, 9.98; N, 6.96; Cl, 17.35.

1,7,7-Trimethyl-2-exo-hydroxy-3-exo-N-methylaminobicyclo[2.2.1]heptane

A mixture of 12.8 g. (0.075 mole) 1,7,7-trimethyl-2-exo-hydroxy-3-exo-aminobicyclo[2.2.1]heptane and 37.0 g. (0.5 mole) ethylformate was refluxed until neutral (three hours) and evaporated under reduced pressure yielding 14.4 g. (97%) residue. The residues were mixed with 75 ml. tetrahydrofuran. The resulting reaction mixture was stirred at reflux for four hours. The excess hydride was destroyed with 4 ml. water and the complex was decomposed with 11 ml. 40% potassium hydroxide. The inorganic salts were removed by filtration, the dried organic filtrates were evaporated under reduced pressure and the 12.2 g. of residues which remained were purified by sublimation at 65°C (0.1 mm.) yielding 11.85 g. (92.2%) of product, m.p. 60-62°C.

Anal. Calcd. for $C_{11}H_{21}NO$: C, 72.07; H, 11.55; N, 7.64. Found: C, 71.79; H, 11.81; N, 7.98.

1,7,7-Trimethyl-2-exo-hydroxy-3-exo-N,N-dimethylaminobicyclo[2.2.1]heptane

A mixture of 11.0 g. (0.06 mole) 1,7,7-trimethyl-2-exo-hydroxy-3-exo-N-methylaminobicyclo[2.2.1]heptane and 25 ml. (0.33 mole) ethyl formate was refluxed for twenty hours, and evaporated under reduced pressure. The residues were triturated under Skelly B, filtered and dried yielding 12.1 g. (95.6%) of product, m.p. 128-130°. The above solids (0.055 mole) were dissolved in 125 ml. tetrahydrofuran and added to a stirred suspension of 5.0 g. (0.13 mole) lithium aluminum hydride in 75 ml. tetrahydrofuran and the resulting mixture was stirred at reflux for five hours. The excess hydride was destroyed with 3 ml. water and the complex was decomposed with 13 ml. 40% potassium hydroxide. The inorganic salts were removed by filtration and the dried filtrates were evaporated and the residues were fractionated under reduced pressure yielding 9.9 g. (91.5%) of product, b.p. 97-98°C (2.5 mm.).

Anal. Calcd. for $C_{12}H_{23}NO$: C, 66.96; H, 11.75; N, 7.10. Found: C, 69.35; H, 11.18; N, 7.05.

Infrared spectrum displayed only bonded OH absorption at 2.98 μ when determined in dilute carbon tetrachloride solution.

1,7,7-Trimethyl-2-exo-benzilyloxy-3-exo-N,N-dimethylaminobicyclo[2.2.1]heptane Hydrochloride, ACC 7121-19

A mixture consisting of 4.92 g. (0.025 mole) 1,7,7-trimethyl-2-exo-hydroxy-3-exo-N,N-dimethylaminobicyclo[2.2.1]heptane and 1.20 g. (0.025 mole) 50% sodium hydride in 100 ml. dry toluene was stirred and refluxed for two hours. The reaction mixture was cooled to below 35°C and a solution of 6.67 g. (0.025 mole) g-chlorodiphenylacetyl chloride in 50 ml. dry toluene was added all at once, and the resulting mixture was stirred at reflux for three hours. After cooling,

50 ml. (5%) sodium bicarbonate solution was added with stirring; and the toluene layer was separated from the aqueous layer. The organic phase was washed with an additional 25 ml. of sodium bicarbonate solution, dried over anhydrous potassium carbonate, filtered and evaporated under reduced pressure leaving 9.1 g. (88.5%) of an oily residue which was dissolved in ethyl ether, and acidified with ethereal hydrochloric acid. The ether was removed by decantation and the residue was dissolved in 150 ml. hot ethylacetate. A small amount of insoluble material was removed by filtration. The filtrate was evaporated to dryness under reduced pressure; and the glassy residue was dissolved in 100 ml. of water and warmed on a steam bath for 15 minutes, at which time a white solid precipitate separated. The solid was collected by filtration, dried and recrystallized from 300 ml. hot acetonitrile yielding 3.66 g., m.p. 290-291°C. The filtrates were evaporated to one third volume under reduced pressure and additional solids collected, 1.2 g. m.p. 285-286°C. These two fractions were combined and suspended twice in boiling water, filtered and dried yielding 3.68 g. (34%) m.p. 294-296°C.

Anal. Calcd. for $C_{26}H_{34}ClNO_3$: C, 70.33; H, 7.90; N, 3.15.
Found: C, 70.17; H, 7.83; N, 3.17.

Norcamphor-morpholine Enamine

A mixture of 110.15 g. (1.0 mole) norcamphor, 174.4 g. (2.0 mole) morpholine and 300 ml. dry toluene was refluxed in an atmosphere of nitrogen until no more water evolution was detected in a Dean-Stark separator. The solvents were removed and the residues distilled under reduced pressure yielding 34.8 g. (19.5%) of product, b.p. 135-137°C (21 mm.).

Anal. Calcd. for $C_{11}H_{17}NO$: N, 7.81. Found: N, 7.14.

Norcamphor Oxime p-Toluenesulfonate

A solution of 3.0 g. (0.024 mole) norcamphor oxime in 80 ml. anhydrous benzene was stirred rapidly in an atmosphere of dry nitrogen while 1.05 g. (0.024 mole) sodium amide was added and the temperature maintained at 25-35°C. The mixture was stirred at room temperature overnight and the solids were collected by filtration, washed well with anhydrous benzene and dried under a nitrogen stream.

To a suspension of the above prepared sodium anion in 100 ml. anhydrous benzene was added a solution of 4.0 g. (0.02 mole) p-toluenesulfonyl chloride in 70 ml. anhydrous benzene and the resulting mixture stirred at room temperature for two hours. The solids were removed by filtration and washed well with benzene. The filtrates were freeze-dried and the residues purified by crystallization from chloroform-Skelly B. The solids were collected by filtration and dried under reduced pressure yielding 2.5 g. (44.6%) of impure product. Further

purification was not attempted due to the instability of the product.

Anal. Calcd. for $C_{14}H_{17}NO_3S$: C, 60.19; H, 6.13; N, 5.01; S, 11.47.
Found: C, 56.78; H, 6.94; N, 4.85; S, 10.62.

3-Formyl Bicyclo[2.2.1]heptan-2-one

To a stirred suspension of 24.0 g. (0.5 mole) sodium hydride (50%) and 200 ml. anhydrous ether at $0^{\circ}C$ was added a solution consisting of 55.0 g. (0.5 mole) norcamphor, 45.0 g. (0.6 mole) ethyl formate, 5 ml. ethanol, and 800 ml. anhydrous ether. The mixture was stirred for three hours, after which 200 ml. water was added. The aqueous layer was separated, extracted twice with ethyl ether, and acidified with 30.0 g. (0.5 mole) acetic acid. The product was extracted into ether, dried over magnesium sulfate and collected by distillation yielding 34.8 g. (50.3%), b.p. $80-82^{\circ}C$ (2 mm.).

exo-3-(N,N-Dimethylaminomethyl)bicyclo[2.2.1]heptan-2-one

Procedure A. To 13.8 g. (0.1 mole) 3-formyl bicyclo[2.2.1]heptan-2-one dissolved in 100 ml. ethanol at $5-10^{\circ}C$ was added 25 ml. (4N) ethanolic dimethylamine. The above alcohol solution, 6.0 g. (0.1 mole) acetic acid and 0.1 g. platinum oxide were placed in a Parr hydrogenator and reduced under 60 psi hydrogen for five hours. The catalyst was filtered off through Celite, and the filtrate evaporated to dryness. The residue was dissolved in 75 ml. water, saturated with potassium carbonate, and the product extracted into ether. The combined extracts were dried over potassium carbonate and the product was collected by distillation yielding 10.9 g., b.p. $85-88^{\circ}C$ (2 mm.).

The acid maleate salt was prepared by treating the base with an equal molar amount of maleic acid in tetrahydrofuran, and purifying the resulting salt by recrystallization from acetonitrile. The product obtained had a m.p. of $151-152^{\circ}C$.

Anal. Calcd. for $C_{14}H_{21}NO_5$: C, 59.34; H, 7.47. Found: C, 59.49; H, 7.46.

Procedure B. A mixture consisting of 27.5 g. (0.25 mole) norcamphor, 31 ml. (0.25 mole) 40% aqueous dimethylamine, 30 ml. (0.25 mole) 37% formaldehyde and 25 ml. (0.25 mole) concentrated hydrochloric acid was stirred at reflux for twenty hours. Upon cooling the reaction mixture was washed twice with 75 ml. portions of ethyl ether, neutralized and saturated with potassium carbonate with cooling. The organic materials were extracted into ethyl ether and the dried ether extracts evaporated and the residues distilled under reduced pressure yielding 17.0 g. (40%) of product, boiling at $85-88^{\circ}C$ (2.3 mm.).

A sample of base was converted to the maleate salt, m.p. $151-152^{\circ}C$. This derivative was in every respect identical to the product from Procedure A as determined by infrared spectral comparison and mixed melting point.

exo-3-(N,N-Dibenzylaminomethyl)bicyclo[2.2.1]heptan-2-one

A mixture of 8.3 g. (0.06 mole) 3-formyl bicyclo[2.2.1]heptan-2-one, 11.8 g. (0.06 mole) dibenzylamine, 100 ml. ethanol and 0.3 g. platinum oxide was placed in a Parr hydrogenator and heated to 50°C under 60 psi hydrogen for five hours. The catalyst was removed by filtration through Celite, and the filtrates were evaporated to dryness. The residue was triturated with hot Skelly B, filtered, dried in the vacuum oven at 60°C, yielding 11.9 g. (62.4%), m.p. 95-97°C.

The identical product was obtained using dibenzylamine and formaldehyde and norcamphor according to the conditions described for the dimethyl derivative (See Procedure B).

Anal. Calcd. for $C_{22}H_{25}NO$: C, 82.73; H, 7.89; N, 4.39. Found: C, 82.44; H, 7.82; N, 4.62.

exo- and endo-3-(N,N-Dimethylaminomethyl)bicyclo[2.2.1]heptan-2-ol

To a suspension of 7.8 g. (0.2 mole) lithium aluminum hydride in 100 ml. tetrahydrofuran was added a solution of 10.9 g. (0.065 mole) 3-(N,N-dimethylaminomethyl)bicyclo[2.2.1]heptan-2-one dissolved in 100 ml. tetrahydrofuran and the mixture was refluxed for four hours. The excess hydride was decomposed with 5 ml. water, and the complex was hydrolyzed with 17 ml. (40%) potassium hydroxide. The inorganic salts were removed by filtration, and the filtrates dried over potassium carbonate. The product was collected by distillation yielding 4.4 g. (40%), b.p. 115-117°C (0.6 mm.).

The distillates were carefully refractionated through a 15" Stedman column under reduced pressure. Two fractions were obtained.

Fraction 1, 67°C(1.0 mm.) - remains a liquid (17%)

Fraction 2, 92°C(1.0 mm.) - solidified upon cooling (83%)

Fraction 1 was converted to the hydrochloride salt using anhydrous hydrochloric acid in ether. Recrystallization from ethanol afforded an analytical sample in 62.4% yield, m.p. 218-219°C.

Anal. Calcd. for $C_{10}H_{20}ClNO$: C, 58.38; H, 9.80. Found: C, 58.43; H, 9.93.

The configuration of the hydroxyl group was shown to be exo and cis to the aminomethyl by infrared hydrogen bonding studies on the free base. The compound exhibited only bonded O-H at 3.05μ , the intensity of which shows no change upon dilution.

Fraction 2 was similarly converted to the hydrochloride salt and purified by recrystallization from acetonitrile, affording the pure product in 73.0% yield, m.p. 222-223°C.

Anal. Calcd. for $C_{10}H_{20}ClNO$: C, 58.38; H, 9.80. Found: C, 58.46; H, 9.81.

Hydrogen bonding studies in the infrared produced absorption bands for both free OH at 2.76μ and bonded O-H at 2.95μ and 3.15μ . The intensity of the free O-H band at 2.76μ increased consistently upon dilution. This has been accepted as proof for the endo and trans (to the aminomethyl group) configuration of the hydroxyl.

endo-2-Hydroxy-exo-3(N,N-dibenzylaminomethyl)bicyclo[2.2.1]heptane Hydrochloride, ACC 7121-48

A solution of 127.5 g. (0.4 mole) exo-3(N,N-dibenzylaminomethyl)-bicyclo[2.2.1]heptan-2-one and 350 ml. of tetrahydrofuran was added dropwise to a refluxing suspension of 15.2 g. (0.4 mole) lithium aluminum hydride in 350 ml. tetrahydrofuran and the resulting mixture was stirred at reflux for four hours. The excess hydride was decomposed with 10 ml. water, and the complex was hydrolyzed with 100 ml. 40% potassium hydroxide. The inorganic salts were removed by filtration, and the filtrates dried over anhydrous potassium carbonate. A mixture of isomers was obtained by distillation yielding 107.8 g. (83.5%) b.p. $155-161^{\circ}\text{C}$ (.02 mm.). The distillates were triturated in 100 ml. Skelly B and the solids were collected by filtration yielding 84.1 g. (65.5%) of product, (m.p. $80-82^{\circ}\text{C}$), which was purified by recrystallization from 120 ml. Skelly B yielding 73.4 g. (57.4%) of product, m.p. $81-83^{\circ}\text{C}$. All Skelly B mother liquors contain the cis isomer which are discussed as ACC 7121-50.

The pure product (5 g., 0.015 mole) was dissolved in anhydrous ethyl ether and acidified with anhydrous hydrogen chloride. The solids which formed were collected by filtration yielding 5.6 g. (100%) of product which was recrystallized from ethyl acetate yielding 3.3 g. (60%) of pure product, m.p. $209-211^{\circ}\text{C}$.

Anal. Calcd. for $\text{C}_{22}\text{H}_{28}\text{ClNO}$: C, 73.81; H, 7.88; N, 3.91; Cl, 9.90.
Found: C, 74.00; H, 8.04; N, 3.83; Cl, 9.72.

The relative configuration of the hydroxyl to the aminomethyl group was determined by hydrogen bonding studies in the infrared. This compound exhibits both bands for free O-H at 2.75μ and bonded O-H at 2.86μ . The intensity of the free OH band at 2.76μ increased upon dilution while bonded O-H band was no longer detectable.

exo-2-Hydroxy-exo-3(N,N-dibenzylaminomethyl)bicyclo[2.2.1]heptane Hydrochloride, ACC 7121-50

The Skelly B mother liquors from the previous procedure, ACC 7121-48, were evaporated yielding 25.0 g. (20.5%) of crude base which was dissolved in anhydrous ethyl ether and acidified with anhydrous hydrogen chloride. The solids which formed were collected by filtration yielding 26.4 g. (96%) and purified by recrystallization from ethyl acetate yielding 9.0 g. (31.5%) of product, m.p. $200-203^{\circ}\text{C}$.

Anal. Calcd. for $\text{C}_{22}\text{H}_{28}\text{ClNO}$: C, 73.81; H, 7.88; N, 3.91; Cl, 9.90.
Found: C, 73.48; H, 7.75; N, 3.88; Cl, 9.92.

The relative configuration of the hydroxyl to the aminomethyl group was determined by hydrogen bonding studies in the infrared. This compound exhibits both bands for free O-H at 2.75μ and bonded O-H at 3.03μ . The intensity of the bonded O-H band at 3.03μ remains the same upon dilution while the free O-H at 2.75μ is very weak.

endo-2-Hydroxy-exo-3(N-benzylaminomethyl)bicyclo[2.2.1]heptane Hydrochloride, ACC 7121-42

A mixture of 16.07 g. (0.05 mole) exo-3(N,N-dibenzylaminomethyl)-bicyclo[2.2.1]heptan-2-ol, 46.4 g. (0.05 mole) 10% hydrochloric acid and 50 ml. water in the presence of 0.5 g. 10% palladium on carbon catalyst was reduced in the Parr hydrogenation apparatus at 60 psi hydrogen at room temperature until the uptake of hydrogen ceased. The catalyst was removed by filtration and the filtrates were evaporated under reduced pressure yielding 12.2 g. (91%) of crude solids, m.p. $242-247^{\circ}\text{C}$. The solids (3.0 g.) were recrystallized from 350 ml. hot acetonitrile and the precipitate which formed on cooling were collected by filtration yielding 2.0 g. of pure product, m.p. $253-255^{\circ}\text{C}$.

Anal. Calcd. for $\text{C}_{15}\text{H}_{22}\text{ClNO}$: C, 67.27; H, 8.28; N, 5.23. Found: C, 67.43; H, 8.18; N, 5.45.

endo-2-Hydroxy-exo-3(aminomethyl)bicyclo[2.2.1]heptane Hydrochloride-ACC 7121-46

A solution of 8.2 g. (0.037 mole) of endo-2-hydroxy-exo-3(N-benzylaminomethyl)bicyclo[2.2.1]heptane hydrochloride in 150 ml. 66% ethanol was reduced in the presence of 0.5 g. 10% palladium on carbon catalyst on the Parr hydrogenation apparatus at 60 psi hydrogen at 40°C until the uptake of hydrogen ceased. The catalyst was removed by filtration and the filtrates were evaporated under reduced pressure yielding 6.3 g. of crude residues. The residues were purified by dissolving in ethanol, treating with Darco, filtering and diluting of the mother liquors with Skelly B. The solids which formed were collected by filtration yielding 4.1 g. (61.6%) of pure product, m.p. 245°C .

Anal. Calcd. for $\text{C}_8\text{H}_{13}\text{ClNO}$: C, 54.07; H, 9.02; N, 7.89; Cl, 19.97. Found: C, 54.20; H, 9.00; N, 7.78; Cl, 19.51.

(mixture of endo and exo)-2-Acetoxy-exo-3(N,N-dimethylaminomethyl)-bicyclo[2.2.1]heptane Hydrochloride, ACC 7121-36

A mixture of 16.8 g. (0.1 mole) 3(N,N-dimethylaminomethyl)bicyclo[2.2.1]heptan-2-ol (isomeric mixture) and 20.4 g. (0.2 mole) acetic anhydride was heated on a steam bath for 6.5 hours. Upon cooling the reaction mixture was poured into ice-water and neutralized with sodium carbonate and extracted repeatedly with ethyl ether. The ether extracts were dried over anhydrous sodium sulfate, filtered, the ether was removed by distillation and the residues were fractionated, yielding 4.25 g. (20.4%), b.p. $107-108^{\circ}\text{C}$ (4.3 mm.).

The aqueous phase was almost saturated with sodium bicarbonate, covered with ether and saturated with potassium hydroxide in the cold. The alkaline phase was extracted repeatedly with ethyl ether, the extracts were dried over anhydrous potassium carbonate, filtered and the ether removed by distillation. The residues were fractionated under reduced pressure. The additional product boiling at 104-105°C (3.3 mm.) was obtained in 61.6% yield (12.8 g.). The yield of combined product was 82.0%.

Anal. Calcd. for $C_{12}H_{21}NO_2$: N, 6.63. Found: N, 6.61.

The ester (15.0 g., 0.074 mole) was dissolved in anhydrous ethyl ether and acidified with anhydrous hydrogen chloride. The solids which formed were collected by filtration and recrystallized from acetonitrile yielding 7.2 g. (40.5%) of product, m.p. 169-170°C.

Anal. Calcd. for $C_{12}H_{22}ClNO_2$: C, 58.15; H, 8.95; N, 5.66. Found: C, 58.63; H, 8.89; N, 5.77.

endo-2-(Benzilyloxy)-exo-3(N,N-dimethylaminomethyl)bicyclo[2.2.1]-heptane Hydrochloride, ACC 7121-40

A solution of 7.5 g. (0.0445 mole) endo-2-hydroxy-exo-3(N,N-dimethylaminomethyl)bicyclo[2.2.1]heptane in 40 ml. dry benzene was added slowly to a mixture of 11.8 g. (0.0445 mole) α -chlorodiphenylacetyl chloride in 100 ml. dry benzene and the resulting mixture was stirred at room temperature over night. The solids were removed by filtration and the filtrates were evaporated under reduced pressure. The residues were dissolved in tetrahydrofuran and stirred with aqueous sodium bicarbonate at room temperature. The organic fraction was washed with saturated sodium chloride, dried, evaporated and the residues triturated in hot Skelly B. The solids which formed on cooling were collected by filtration yielding 7.2 g. (42.5%) of product, m.p. 62-64°C. The solids were dissolved in anhydrous ethyl ether and acidified with anhydrous hydrogen chloride. The crude salt was recrystallized repeatedly from isopropanol yielding 2.1 g. (26.8%) of product, m.p. 147-148°C.

Anal. Calcd. for $C_{24}H_{30}ClNO_3$: C, 69.29; H, 7.27; O, 11.54. Found: C, 69.3; H, 7.4; O, 11.7.

endo-2-Benzilyloxy-exo-3(N,N-dibenzylaminomethyl)bicyclo[2.2.1]heptane Hydrochloride, ACC 7121-47

A mixture of 32.1 g. (0.1 mole) endo-2-hydroxy-exo-3(N,N-dibenzylaminomethyl)bicyclo[2.2.1]heptane, 24.2 g. (0.1 mole) methyl benzilate and 500 ml. n-heptane was heated to reflux in the presence of sodium methoxide until the separation of methanol in a Dean-Stark separator ceased. Upon cooling the reaction mixture was filtered and washed with water until the washes were neutral. The dried organic fractions were evaporated under reduced pressure yielding 50.0 g. (94%) of a heavy oil. The residues were dissolved in ethyl ether and acidified

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with anhydrous hydrogen chloride. The solids which formed were collected by filtration yielding 58.5 g. (103%) of crude product, m.p. 120-124°C. The crude product was purified by recrystallization from 300 ml. hot ethanol yielding 29.4 g. (51.7%) of product, m.p. 210-211°C.

Anal. Calcd. for $C_{36}H_{38}ClNO_3$: C, 76.11; H, 6.74; N, 2.47; Cl, 6.24. Found: C, 76.2; H, 6.6; N, 2.52; Cl, 6.36.

endo-2-Benzilyloxy-exo-3-aminomethyl-bicyclo[2.2.1]heptane, ACC 7121-53

A solution of 11.7 g. (0.02 mole) endo-2-benzilyloxy-exo-3(N,N-dibenzylaminomethyl)bicyclo[2.2.1]heptane hydrochloride, 200 ml. ethanol and 100 ml. water was reduced on a Parr hydrogenation apparatus at 60 psi hydrogen at 40°C in the presence of 0.2 g. 10% palladium on carbon catalyst until the uptake of hydrogen ceased. The catalyst was removed by filtration and the filtrates were evaporated under reduced pressure. The residues were dissolved in water, saturated with sodium bicarbonate and the base extracted into ether, dried and the solvents removed under reduced pressure. The residues (4.5 g.) were purified by recrystallization from normal heptane yielding 3.25 g. (46.0%) of product, m.p. 123-124°C.

Anal. Calcd. for $C_{22}H_{25}NO_3$: C, 75.1; H, 7.2; N, 4.0. Found: C, 74.8; H, 7.3; N, 3.8.

endo-2-Hydroxy-2-phenyl-exo-3(N,N-dimethylaminomethyl)bicyclo[2.2.1]heptane Acid Maleate, ACC 7121-33

A solution of 16.7 g. (0.1 mole) exo-3(N,N-dimethylaminomethyl)bicyclo[2.2.1]heptan-2-one in 100 ml. anhydrous ethyl ether was added to 0.12 mole phenyl lithium (obtained as a benzene ether solution from Foote) at 20°C \pm 3°C and stirred at reflux for two and one half hours. The reaction mixture was diluted with ether and poured into ice water. After extracting with saturated sodium chloride, the dried organic fraction was evaporated under reduced pressure. The drying agent was washed well with methanol and the washes also evaporated under reduced pressure. All the residues were combined and triturated under Skelly B, the solids isolated by filtration and recrystallized from hot Skelly B yielding 8.4 g. (86.6%) of pure trans isomer, m.p. 97-98°C.

Anal. Calcd. for $C_{18}H_{23}NO$: C, 78.32; H, 9.44; N, 5.71. Found: C, 78.57; H, 9.51; N, 5.59.

All Skelly B mother liquors contain the cis isomer which are discussed as ACC 7121-34.

Acid Maleate Salt. Maleic acid (2.36 g., 0.02 mole) was dissolved in 200 ml. anhydrous ethyl ether and added to an ethereal solution of 5.1 g. (0.02 mole) of the base. The solids which formed were collected by filtration and recrystallized from 125 ml. hot acetonitrile yielding 5.65 g. (82.5%) of product, m.p. 191-193°C.

Anal. Calcd. for $C_{20}H_{27}NO_5$: C, 66.47; H, 7.53; N, 3.88. Found: C, 66.29; H, 7.41; N, 3.94.

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The relative configuration of the hydroxyl to the aminomethyl groupings was determined by hydrogen bonding studies in the infrared. This compound exhibits both bands for free O-H at 2.77μ and bonded O-H at 2.90μ . The intensity of the free OH bands at 2.77μ increase upon dilution.

exo-2-Hydroxy-2-phenyl-exo-3(N,N-dimethylaminomethyl)bicyclo[2.2.1]-heptane Acid Maleate, ACC 7121-34

The Skelly B mother liquors from the previous procedure were evaporated and the residues distilled under reduced pressure yielding 6.8 g. (27.7%) of heavy viscous liquid, b.p. $104-107^{\circ}\text{C}$ (0.012 mm.).

Acid Maleate Salt. Maleic acid (2.36 g., 0.02 mole) was dissolved in 200 ml. anhydrous ethyl ether and added to an ethereal solution of 5.1 g. (0.02 mole) of liquid isomer. The solids which formed were collected by filtration yielding 5.4 g. (72.3%) of product, m.p. $123-124^{\circ}\text{C}$. All of the product was dissolved in 50 ml. hot acetonitrile and the solids which formed were collected by filtration yielding 2.05 g. (38.0%) of product, m.p. $188-190^{\circ}\text{C}$ (salt of solid isomer). The mother liquors were evaporated and the residues recrystallized from 65 ml. hot ethyl acetate. The solids which formed were collected by filtration yielding 2.3 g. (42.7%) of product, m.p. $138-140^{\circ}\text{C}$. Further recrystallization from 200 ml. ethyl acetate raised the m.p. only one degree.

Anal. Calcd. for $\text{C}_{20}\text{H}_{27}\text{NO}_5$: C, 66.47; H, 7.53; N, 3.88. Found: C, 66.18; H, 7.50; N, 3.62.

The relative configuration of the hydroxyl to the aminomethyl group was determined by hydrogen bonding studies in the infrared. This compound exhibits only a band for bonded OH at 3.05μ , the intensity of which does not change upon dilution.

endo-2-Hydroxy-2-phenyl-exo-3(N,N-dibenzylaminomethyl)bicyclo[2.2.1]-heptane Hydrochloride, ACC 7121-58

A solution of 31.95 g. (0.10 mole) exo-3(N,N-dibenzylaminomethyl)-bicyclo[2.2.1]heptane-2-one in 200 ml. tetrahydrofuran was added to 135 ml. (0.12 mole) of 0.95 molar phenyl lithium in benzene-ether solution at $20^{\circ}\text{C} \pm 3^{\circ}\text{C}$. The mixture was stirred one hour additional at room temperature and refluxed with stirring for eleven hours. Upon cooling the reaction mixture was poured into 125 ml. ice-water and saturated with sodium chloride. The aqueous fraction was washed with ether and the organic phases combined, dried, filtered and evaporated under reduced pressure. The residues (43 g., 108%) were dissolved in anhydrous ethyl ether and acidified with anhydrous hydrogen chloride. The solids which formed were collected by filtration yielding 47.0 g. of product. Recrystallization from hot acetonitrile afforded 28.5 g. (65.7%) of slightly impure trans isomer. The mother liquors from the isolation of this material were evaporated under reduced pressure and the residues were suspended in hot benzene and collected by filtration yielding 5.15 g. of product, m.p. $160-165^{\circ}\text{C}$.

Recrystallization from ethyl acetate yielded 3.52 g. (70.0% recovery) of pure trans isomer, m.p. 133-136°C.

Anal. Calcd. for $C_{28}H_{32}ClNO$: C, 77.48; H, 7.20; N, 3.23. Found: C, 77.25; H, 7.60; N, 3.19.

The relative configuration of the hydroxyl to the amino methyl group was determined by hydrogen bonding studies in the infrared. This compound exhibits both bands for free O-H at 2.77μ and bonded O-H at 2.88μ . The intensity of the free O-H bonds at 2.77μ increased upon dilution.

exo-2-Hydroxy-2-phenyl-exo-3(N,N-dibenzylaminomethyl)bicyclo[2.2.1]-heptane Hydrochloride.

The mother liquors after isolation of the above trans isomer were combined and evaporated under reduced pressure. The residues were triturated in hot benzene and the solids which formed were collected by filtration from the hot benzene solution. These solids proved to be more trans isomer. The solids which formed in the filtrates on cooling were collected by filtration, washed with ethyl ether and purified by recrystallization from hot isopropanol yielding 0.76 g. of pure cis isomer, m.p. 184-186°C.

Anal. Calcd. for $C_{28}H_{32}ClNO$: C, 77.48; H, 7.20. Found: C, 76.98; H, 7.60.

The relative configuration of the hydroxyl to the amino methyl groupings was determined by hydrogen bonding studies in the infrared. This compound exhibits a band for bonded OH at 3.00μ , the intensity of which does not change upon dilution.

endo-2-Hydroxy-2-phenyl-exo-3-aminomethylbicyclo[2.2.1]heptane-Hydrochloride, ACC 7121-56

A.- A solution of 10.0 g. (0.023 mole) endo-2-hydroxy-2-phenyl-exo-3(N,N-dibenzylaminomethyl)bicyclo[2.2.1]heptane hydrochloride in 100 ml. 70% ethanol was reduced in a Parr hydrogenation apparatus at 60 psi hydrogen at room temperature in the presence of 0.2 g. 10% palladium on carbon catalyst until the uptake of hydrogen ceased. The catalyst was removed by filtration and the filtrate was evaporated under reduced pressure. The frothy residues (5.5 g.) were warmed in acetonitrile and the resulting white solids were collected by filtration yielding 4.6 g. (78.8%) of product, m.p. 228-229°C.

B.- A solution of 13.0 g. (0.03 mole) of the dibenzyl compound was treated as in run A but the reduction was carried out at 50°C. The reaction products were isolated yielding 7.0 g. gum which was crystallized by refluxing in ethyl acetate. The solids were collected by filtration yielding 5.9 g. (77.6%) of product, m.p. 229-230°C. Infrared spectra of both the salts and released bases from A and B were identical. All the solids from A and B were combined yielding 10.5 g. (78.2%) of product, m.p. 229-230°C.

Anal. Calcd. for $C_{14}H_{20}ClNO$: C, 66.25; H, 7.94; N, 5.52; Cl, 13.97.
Found: C, 66.18; H, 7.96; N, 5.51; Cl, 13.91.

exo-3(N,N-Dimethylaminomethyl)bicyclo[2.2.1]heptan-2-one Oxime,
ACC 7121-51

A mixture of 16.7 g. (0.100 mole) exo-3(N,N-dimethylaminomethyl)-bicyclo[2.2.1]heptan-2-one, 7.0 g. (0.105 mole) hydroxylamine hydrochloride and 8.0 ml. (0.100 mole) pyridine was refluxed in 170 ml. ethanol for two hours and then evaporated under reduced pressure. The residues were stirred for 8 hours with 5.3 g. (0.050 mole) sodium bicarbonate in 100 ml. water and the solids which formed were collected by filtration and dried yielding 12.8 g. (68.6%) of crude product, m.p. 188-190°C. The solids were purified by recrystallization from 400 ml. ethanol yielding 6.85 g. (36.8%) of pure product, m.p. 204-205°C.

Anal. Calcd. for $C_{10}H_{18}N_2O$: C, 65.88; H, 9.95; N, 15.37. Found: C, 65.95; H, 10.22; N, 15.50.

exo-3(N,N-Dibenzylaminomethyl)bicyclo[2.2.1]heptan-2-one Oxime
Hydrochloride, ACC 7121-52

A mixture of 31.9 g. (0.100 mole) exo-3(N,N-dibenzylaminomethyl)-bicyclo[2.2.1]heptan-2-one, 7.0 g. (0.105 mole) hydroxylamine hydrochloride and 170 ml. ethanol was refluxed for two hours and evaporated under reduced pressure. The residues were stirred in 170 ml. 5% sodium bicarbonate for several hours and the solids collected by filtration yielding 51.2 g. (137.0%) of crude product, m.p. 185-188°C. The solids were recrystallized from 1400 ml. hot isopropanol yielding 11.4 g. (30.4%) of pure product, m.p. 219-220°C.

Anal. Calcd. for $C_{22}H_{27}ClN_2O$: C, 71.24; H, 7.34; N, 7.55; Cl, 9.56.
Found: C, 71.37; H, 7.44; N, 7.45; Cl, 9.62.

exo-3(N,N-Dimethylaminomethyl)bicyclo[2.2.1]heptan-2-one Oxime
Methyliodide, ACC 7121-55

A mixture of 12.2 g. (0.67 mole) exo-3(N,N-dimethylaminomethyl)-bicyclo[2.2.1]heptan-2-one oxime and 9.5 g. (0.067 mole) methyl iodide was stirred in 250 ml. acetone at room temperature for sixteen hours. The solids were collected by filtration to yield 20.3 g. (93.5%) of product, m.p. 245-247°C. The salt (4.0 g.) was further purified by recrystallization from 125 ml. ethanol yielding 3.05 g. (76.5% recovery) of product, m.p. 249-250°C.

Anal. Calcd. for $C_{11}H_{21}N_2OI$: C, 40.74; H, 6.53; N, 8.65. Found: C, 40.85; H, 6.52; N, 8.66.

N-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-2-(4-methyl-1-piperazinyl)acetamide, ACC 7121-49

A mixture of 11.6 g. (0.041 mole) 2-chloro-N-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)acetamide, 8.1 g. (0.081 mole) N-methyl piperazine, and 130 ml. absolute ethyl alcohol was heated in a stirred autoclave at 120°C for 22 hours. The cooled solution was evaporated under reduced pressure and the heavy oil dissolved in ethyl ether and washed with saturated potassium hydroxide and water. The dried extracts were evaporated under reduced pressure yielding 10.7 g. (76.5%) of crude product, m.p. 119-123°C. The crude material was recrystallized from 970 ml. Skelly B yielding 8.3 g. (60%) of product, m.p. 128-130°C.

Anal. Calcd. for $C_{22}H_{27}N_3O$: C, 75.60; H, 7.64; N, 11.83. Found: C, 75.36; H, 7.79; N, 12.03.

5-(4-Morpholinoethylamino)-10,11-dihydro-5H-dibenzo[a,d]cycloheptene
Dihydrochloride, ACC 7121-31

Anhydrous hydrogen chloride was bubbled through a cooled solution of 10.5 g. (0.05 mole) 10,11-dihydro-5H-dibenzo[a,d]cycloheptene-5-ol in dry benzene for one hour. The solution was dried over anhydrous calcium chloride, filtered and evaporated under reduced pressure. The residues were dissolved in 125 ml. dry toluene and added in one portion to 13.0 g. (0.10 mole) 4-morpholinoethylamine in 100 ml. dry toluene and the mixture stirred at reflux for six hours. Upon cooling the mixture was washed with saturated potassium hydroxide, the dried organic fraction evaporated and the residues distilled under reduced pressure yielding 13.8 g. (85.5%) of product, b.p. 195-198°C, (0.03 mm.). The distillates (0.0425 mole) were dissolved in 300 ml. anhydrous ethyl ether and acidified with anhydrous hydrogen chloride. The solids which formed were collected by filtration and recrystallized from 550 ml. ethanol, treated with Darco and filtered. The solids which formed on

cooling were collected by filtration yielding 6.2 g. (31.4%) of product, m.p. 204°C. Subsequent recrystallizations from ethanol did not alter the m.p. but did reduce the yield due to solvolytic cleavage. Recrystallization of 2.3 g. from 600 ml. acetonitrile yielded 1.9 g. (9.6%) of product, m.p. 208-209°C.

Anal. Calcd. for $C_{21}H_{28}Cl_2N_2O$: C, 63.79; H, 7.14; N, 7.08; Cl, 17.93. Found: C, 63.65; H, 7.07; N, 7.30; Cl, 18.38.

5-[N-Methyl-N-(2-hydroxy-1-ethyl)amino]-10,11-dihydro-5H-dibenzo-[a,d]cycloheptene, ACC 7121-54

A solution of 48.0 g. (0.21 mole) 5-chloro-10,11-dihydro-5H-dibenzo-[a,d]cycloheptene in 200 ml. anhydrous benzene was added rapidly to a stirred solution of 80.0 g. (1.07 mole) of 2-methylaminoethanol in 800 ml. anhydrous benzene and the resulting mixture was stirred at reflux for six hours. The cooled reaction mixture was washed with saturated potassium hydroxide solution, the organic fraction washed with water and dried. The solvents were removed and the residues fractionated under reduced pressure yielding 43.0 g. (77%) of product, b.p. 170-175°C (0.04 mm.), infrared (CCl_4) 2.83μ (OH).

Anal. Calcd. for $C_{18}H_{21}NO$: C, 80.89; H, 7.92; N, 5.24. Found: C, 80.72; H, 8.19; N, 5.16.

5-(4-β-Hydroxyethyl-1-piperaziny)-10,11-dihydro-5H-dibenzo[a,d]-cycloheptene

Anhydrous hydrogen chloride was bubbled through a cooled solution of 10.5 g. (0.05 mole) 10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ol in 100 ml. anhydrous benzene for one hour. The solution was dried over anhydrous calcium chloride, filtered and evaporated under reduced pressure. The residues were dissolved in 100 ml. dry toluene and added in one portion to a stirred solution of 65.1 g. (0.5 mole) β-hydroxyethyl piperazine in 700 ml. anhydrous toluene and the mixture was stirred at reflux for six hours. Upon cooling the mixture was washed with saturated potassium hydroxide, the dried organic fraction evaporated and the residues distilled under reduced pressure yielding 9.8 g. (60.8%) of product, b.p. 195-197°C (0.02 mm.).

Anal. Calcd. for $C_{21}H_{26}N_2O$: N, 8.69. Found: N, 8.56.

5-[β-(N-Methylamino)ethoxy]-10,11-dihydro-5H-dibenzo[a,d]cycloheptene Acid Maleate, ACC 7121-57

Anhydrous hydrogen chloride was bubbled through a cooled solution of 44.0 g. (0.28 mole) 10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ol in 400 ml. dry benzene for one hour. The reaction mixture was dried over anhydrous calcium chloride, filtered and evaporated under reduced pressure. The residues were dissolved in 200 ml. dry toluene and added in one portion to a stirred solution of 15.2 g. (0.20 mole)

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2-methylaminoethanol in 200 ml. dry toluene and the mixture stirred at reflux for six hours. After cooling the solids which formed were collected by filtration, dissolved in water and saturated with potassium carbonate and the base extracted into ether. The organic fractions were dried, evaporated and the residue purified by fractionation under reduced pressure yielding 6.3 g. (11.8%) of product, b.p. 175-177°C (0.04 mm.), infrared (CCl_4) 3.0μ (NH), 9.38μ (-CH-O-CH₂-). The basic ether (2.3 g., 0.0086 mole) was dissolved in ethyl ether and titrated with an ethereal solution of 0.95 g. (0.0086 mole) maleic acid to pH 5. The resulting white gums crystallized rapidly. The solids were collected by filtration and purified by recrystallization from 550 ml. hot ethyl acetate yielding 2.2 g. (67%) of product, m.p. 144-146°C.

Anal. Calcd. for $\text{C}_{22}\text{H}_{25}\text{NO}_5$: C, 66.92; H, 6.57; N, 3.66. Found: C, 66.79; H, 6.63; N, 3.43.

5-(β -N,N-Dimethylaminoethoxy)-10,11-dihydro-5H-dibenzo[a,d]cycloheptene
Acid Maleate, ACC 7121-21³¹

A mixture of 2.4 g. (0.05 mole) 50% sodium hydride, 10.5 g. (0.05 mole) 10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ol and 100 ml. anhydrous toluene were stirred at reflux for one hour, cooled to 25°C and a solution of freshly distilled β -N,N-dimethylaminoethyl chloride in 50 ml. dry toluene was added and the resulting mixture was stirred at reflux for six hours. Upon cooling, the reaction mixture was washed with 5% sodium bicarbonate and water, the dried organic fractions were evaporated and the residues were distilled under reduced pressure yielding 13.4 g. (95.1%) of product, b.p. 140-143°C (0.2 mm.).

Anal. Calcd. for $\text{C}_{19}\text{H}_{23}\text{NO}$: N, 4.98. Found: N, 4.09.

A solution of 4.2 g. (0.036 mole) maleic acid in 250 ml. ethyl ether was added to a solution of 12.1 g. (0.043 mole) above base in 50 ml. ethyl ether. The solids which formed were collected by filtration yielding 13.6 g. of product, m.p. 94-96°C. The solids were purified by recrystallization from 100 ml. ethyl acetate yielding 11.7 g. (59.0%) of pure product, m.p. 121-122°C.

Anal. Calcd. for $\text{C}_{23}\text{H}_{27}\text{NO}_5$: N, 3.52; N.E., 198.7. Found: N, 3.55; N.E., 202.8.

5-[β -(4-Methyl-1-piperazinyl)ethoxy]-10,11-dihydro-5H-dibenzo[a,d]-
cycloheptene Bis Maleate, ACC 7121-22

Anhydrous hydrogen chloride was bubbled through a cooled solution of 10.5 g. (0.05 mole) 10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ol in 100 ml. dry benzene for 1.5 hours. The solution was dried over anhydrous calcium chloride, filtered and evaporated under reduced pressure. The resulting chloro-compound was dissolved in 50 ml. hot dry xylene and added in one portion to a stirred solution of 14.4 g.

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(0.10 mole) of 1-methyl-4-hydroxyethyl piperazine in 50 ml. dry xylene and the mixture stirred at reflux for three hours. After removing the xylene under reduced pressure, residues were dissolved in water, saturated with sodium bicarbonate and extracted into ether. The dried ether extracts were evaporated, and the residues distilled under reduced pressure, yielding 7.3 g. (43.5%) of product, b.p. 210-216°C (0.02 mm.). The distillates (0.022 mole) were dissolved in 200 ml. anhydrous ethyl ether and the pH was adjusted to 7 with 7 ml. of a solution of 2.55 g. (0.022 mole) maleic acid in 15 ml. ethanol. The white solids which formed were collected by anhydrous filtration and were recrystallized from a refluxing solution of 300 ml. ethyl acetate and 80 ml. ethanol. The solids which formed on cooling were collected by filtration yielding 1.4 g. (11.2%) of product, m.p. 174-175°C.

Anal. Calcd. for $C_{30}H_{38}N_2O_8$: C, 63.36; H, 6.38. Found: C, 63.12; H, 6.26.

5-(1-Methyl-3-piperidyloxy)-10,11-dihydro-5H-dibenzo[a,d]cycloheptene
Acid Fumarate, ACC 7121-26

This compound was prepared by a procedure identical to that for ACC 7121-22 utilizing the appropriate hydroxyalkylamine. The base was purified by distillation under reduced pressure yielding 12.7 g. (82.8%) of product, b.p. 182-185°C (0.02 mm.). The fumaric acid salt was prepared by conventional methods and purified by recrystallization from ethanol.

Anal. Calcd. for $C_{25}H_{29}NO_5$: C, 70.90; H, 6.90; N, 3.31; N.E., 211.7. Found: C, 70.88; H, 7.00; N, 3.55; N.E., 209.5.

5-(1-Methyl-2-pyrrolidylmethoxy)-10,11-dihydro-5H-dibenzo[a,d]cycloheptene
Acid Maleate, ACC 7121-27

This compound was prepared by a procedure identical to that for ACC 7121-22 utilizing the appropriate hydroxyalkylamine. The base was purified by distillation under reduced pressure yielding 11.2 g. (72.8%) of product, b.p. 170-175°C (0.02 mm.). The maleic acid salt was prepared by conventional methods and purified by recrystallization from a mixture of ethyl acetate and ethyl ether.

Anal. Calcd. for $C_{25}H_{29}NO_5$: C, 70.90; H, 6.90; N, 3.31; N.E., 211.7. Found: C, 70.89; H, 7.11; N, 3.23; N.E., 221.9.

5-(1-Methyl-4-piperidyloxy)-10,11-dihydro-5H-dibenzo[a,d]cycloheptene
Acid Fumarate Monohydrate, ACC 7121-30

This compound was prepared by a procedure identical to that for ACC 7121-22 utilizing the appropriate hydroxyalkylamine. The base was purified by distillation under reduced pressure yielding 13.7 g.

(89.2%) of product, b.p. 162-165°C (0.03 mm.). The fumaric acid salt was prepared by conventional methods and purified by recrystallization from acetonitrile.

Anal. Calcd. for $C_{25}H_{31}NO_8$: C, 68.01; H, 7.08; O, 21.75. Found: C, 68.15; H, 6.59; O, 21.2.

5-(3-Quinuclidyloxy)-10,11-dihydro-5H-dibenzo[a,d]cycloheptene,
ACC 7121-38

This compound was prepared by a procedure identical to that for ACC 7121-22 utilizing the appropriate hydroxyalkylamine. The base was purified by distillation under reduced pressure yielding 11.3 g. (67.2%) of product, b.p. 180°C (0.03 mm.). The product, which solidified on standing was recrystallized from 30 ml. hot Skelly B yielding 9.0 g. (53.4%) of crystalline product, m.p. 112-113°C.

Anal. Calcd. for $C_{22}H_{25}NO$: C, 82.78; H, 7.89. Found: C, 82.75; H, 7.97.

O-[β -(N,N-Dimethylamino)ethyl]-10,11-dihydro-5H-dibenzo[a,d]cyclo-
hepten-5-one Oxime Fumarate, ACC 7121-24

A mixture of 4.5 g. (0.02 mole) of 10,11-dihydro-5H-dibenzo[a,d]cycloheptene-5-one oxime and 1.0 g. (0.02 mole) 50% sodium hydride in 100 ml. dry toluene was heated at reflux for one hour. The mixture was cooled to 20°C and 6.4 g. (0.06 mole) of freshly distilled β -N,N-dimethylaminoethyl chloride in 20 ml. dry toluene was added and the resulting mixture was stirred under reflux for three hours. Upon cooling 20 ml. water was added, the layers separated and the organic fractions were washed with water. The dried organic fractions were evaporated under reduced pressure yielding 6.1 g. of oily residue.

The above residue and 2.3 g. (0.02 mole) of fumaric acid were dissolved in 100 ml. ethanol, diluted to the cloud point with 125 ml. ethyl ether and refrigerated. The solids which formed were collected by filtration, triturated under acetone and acetonitrile yielding 3.95 g. (48.2%) of product, m.p. 140-142°C.

Anal. Calcd. for $C_{23}H_{26}N_2O_5$: C, 67.30; H, 6.38; N, 6.82. Found: C, 67.49; H, 6.54; N, 6.82.

O-Carboethoxy-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-one Oxime,
ACC 7121-29

To 2.25 g. (0.01 mole) 10,11-dihydro-5H-dibenzo[a,d]cycloheptene-5-one oxime and 1.00 g. (0.01 mole) triethylamine dissolved in 50 ml.

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dry benzene and cooled to 20°C was added 1.1 g. (0.01 mole) ethyl chloroformate, and the solution was heated under reflux for two hours. Upon cooling the solids were removed by filtration through Celite and the filtrates evaporated under reduced pressure. The residues were triturated under Skelly B, the solids were collected by filtration yielding 2.70 g. (93.0%) of product, m.p. 112-113°C.

Anal. Calcd. for $C_{18}H_{17}NO_3$: C, 73.20; H, 5.80. Found: C, 73.48; H, 5.74.

O-[β -(N-Benzyl-N-methylamino)ethyl]-10,11-dihydro-5H-dibenzo[a,d]-cyclohepten-5-one Oxime Acid Fumarate, ACC 7121-32

This compound was prepared by a procedure identical to that for ACC 7121-24 using the corresponding aminoalkyl halide. The fumaric acid salt was prepared by conventional methods and was purified by recrystallization from isopropanol.

Anal. Calcd. for $C_{28}H_{30}N_2O_5$: C, 71.58; H, 6.21; N, 5.75. Found: C, 71.56; H, 6.15; N, 5.49.

O-[β -(4-Methyl-1-piperazinyl)ethyl]-10,11-dihydro-5H-dibenzo[a,d]-cyclohepten-5-one Oxime Diacid Maleate, ACC 7121-43

This compound was prepared by a procedure identical to that for ACC 7121-24 using the corresponding aminoalkyl halide. The maleic acid salt was prepared by conventional methods and was purified by recrystallization from ethanol.

Anal. Calcd. for $C_{30}H_{35}N_3O_8$: C, 61.95; H, 6.06; N, 7.24; N.E., 145.4. Found: C, 61.98; H, 6.25; N, 7.27; N.E., 146.0.

O-[γ -(N,N-Dimethylamino)propyl]-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-one Oxime Acid Maleate, ACC 7121-59

This compound was prepared by a procedure identical to that for ACC 7121-24 using the corresponding aminoalkyl halide. The maleic acid salt was prepared by conventional methods and was purified by recrystallization from ethyl acetate.

Anal. Calcd. for $C_{24}H_{28}N_2O_5$: C, 67.90; H, 6.65; N, 6.60. Found: C, 67.52; H, 6.91; N, 6.58.

O-[β -(N,N-Dimethylamino)ethyl]-5H-dibenzo[a,d]cyclohepten-5-one Oxime Acid Fumarate, ACC 7121-25

This compound was prepared by a procedure identical to that for ACC 7121-24 using the corresponding oxime and aminoalkyl halide.

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The fumaric acid salt was prepared by conventional methods and recrystallized from ethanol.

Anal. Calcd. for $C_{23}H_{24}N_2O_5$: C, 67.63; H, 5.92; N, 6.86. Found: C, 67.51; H, 5.99; N, 6.87.

3-Chloro-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-one Oxime,
ACC 7121-39

A mixture of 65.3 g. (0.27 mole) 3-chloro-10,11-dihydro-5H-dibenzo-[a,d]cyclohepten-5-one, 56.3 g. (0.81 mole) hydroxylamine hydrochloride and 800 ml. pyridine was stirred at reflux for 12 hours. The solvents were removed under reduced pressure and the residues were covered with one liter of ether and washed with 250 ml. portions of 3N hydrochloric acid, 5% sodium hydroxide and water. The dried organic fraction was evaporated and the residues were triturated in Skelly B and collected by filtration, yielding 49.5 g. (70.6%) of product. Further recrystallization from acetonitrile with Darco treatment yielded 33.5 g. (47.8%) of product, m.p. 198-201°C.

Anal. Calcd. for $C_{15}H_{12}ClNO$: C, 69.91; H, 4.70; N, 5.44; Cl, 13.76. Found: C, 69.91; H, 4.70; N, 5.34; Cl, 13.79.

O-[β -(N,N-Dimethylamino)ethyl]-3-chloro-10,11-dihydro-5H-dibenzo-
[a,d]cyclohepten-5-one Oxime Acid Fumarate, ACC 7121-44

This compound was prepared by a procedure identical to that for ACC 7121-24 using the corresponding oxime and aminoalkyl halide. The fumaric acid salt was prepared by conventional methods and was purified by recrystallization from isopropanol.

Anal. Calcd. for $C_{23}H_{25}ClN_2O_5$: C, 62.08; H, 5.66; N, 6.30; Cl, 7.97. Found: C, 62.25; H, 5.85; N, 6.23; Cl, 7.96.

O-[β -(4-Methyl-1-piperazinyl)ethyl]-3-chloro-10,11-dihydro-5H-dibenzo-
[a,d]cyclohepten-5-one Oxime Fumarate, ACC 7121-45

This compound was prepared by a procedure identical to that for ACC 7121-24 using the corresponding oxime and aminoalkyl halide. The fumaric acid salt was prepared by conventional methods and was purified by recrystallization from ethanol.

Anal. Calcd. for $C_{26}H_{30}ClN_3O_5$: C, 62.45; H, 6.05; N, 8.40; Cl, 7.09. Found: C, 62.45; H, 6.14; N, 8.42; Cl, 7.01.

5,6,11,12-Tetrahydrodibenzo[b,f]azocine

A solution of 24.2 g. (0.104 mole) 10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-one oxime in 200 ml. tetrahydrofuran was added dropwise to a refluxing suspension of 7.8 g. (0.21 mole) of lithium aluminum hydride in 250 ml. tetrahydrofuran and the resulting mixture was stirred at reflux for twenty-four hours. The excess hydride was decomposed with 12 ml. water and the complex was hydrolyzed with 40 ml. 40% potassium hydroxide. The inorganic salts were removed by filtration and washed with tetrahydrofuran. The dried organic filtrates were evaporated under reduced pressure, the residues dissolved in ether and the ether extracted with 5% hydrochloric acid. The acid aqueous fraction was saturated with sodium hydroxide and extracted repeatedly with ether. The dried ether extracts were evaporated under reduced pressure and the residues refluxed in 100 ml. Skelly B. The solids which formed were collected by filtration and dried yielding 10.7 g. (49.3%) of product, m.p. 130-132°C. This product was in every way identical to that prepared according to the procedure of Monro et. al.³⁵

Anal. Calcd. for $C_{15}H_{15}N$: N, 6.70. Found: N, 6.82.

Phenylcyclopentylacetoxy Acetic Acid.

To 22.0 g. (0.1 mole) phenylcyclopentyl glycolic acid in 100 ml. dry benzene was added a solution of 10.2 g. (0.1 mole) acetic anhydride and 25 ml. dry benzene. The mixture was refluxed for two hours, treated with Darco, and concentrated to dryness under vacuum, residue - 23.2 g. (88.6%).

Anal. Calcd. for $C_{15}H_{18}O_4$: N.E., 262.3. Found: N.E., 283.2. The infrared spectrum indicates absence of O-H band, presence of acetate carbonyl at 5.7μ .

Phenylcyclopentyl Ketone

A mixture of 12.1 g. (0.05 mole) methyl phenylcyclopentyl glycolate, 2.4 g. (0.05 mole) 50% sodium hydride and 100 ml. toluene was stirred at reflux for two hours. After the addition of 7.0 g. (0.55 mole) benzyl chloride the mixture was refluxed an additional three hours. Upon cooling, 5 ml. methanol was added and the salts were removed by filtration. The filtrates were evaporated under reduced pressure yielding 16 g. of a mixture of solids and oil. The residues were triturated in Skelly B and the solids were removed by filtration. The filtrates were evaporated and the residues were distilled under reduced pressure yielding 4.3 g. (26.5%) of product, b.p. 170-172°C (0.7 mm.).

VPC comparison of this material with authentic phenylcyclopentyl ketone prepared by the reaction of phenyl cyanide and cyclopentyl magnesium bromide showed that the two compounds had identical elution times.

(-) 1-Ethyl-3-piperidyl-phenylcyclopentyl Glycolate Hydrochloride

L-(1-Ethyl-2-pyrrolidylmethyl)phenylcyclopentyl glycolate hydrochloride (36.8 g., 0.1 mole) (previously prepared as part of the Lakeside research program prior to the initiation of this contract) was dissolved in 200 ml. water, saturated with sodium bicarbonate and extracted with ethyl ether. The dried ether extracts were evaporated, and the residues were distilled under reduced pressure yielding 30.5 g. (92.0%) of ring expanded product, b.p. 139-140°C (0.02 mm.). The base (0.09 mole) was dissolved in acetone and acidified with anhydrous hydrogen chloride. The solids which formed were collected by filtration and purified by recrystallization from acetonitrile yielding 12.2 g. (33.1%) of solids, m.p. 231-232°C.

Anal. Calcd. for $C_{20}H_{30}ClNO_3$: N, 3.81; Cl, 9.66. Found: N, 3.85; Cl, 9.57. α_D^{25} DMF + 9.29°.

(-) Phenylcyclopentyl Glycolic Acid

A mixture of 7.4 g. (0.02 mole) (-) 1-ethyl-3-piperidyl-phenylcyclopentylglycolate hydrochloride, 2.8 g. (0.05 mole) potassium hydroxide, 75 ml. methanol and 5 ml. water was refluxed for three hours and evaporated under reduced pressure. The residues were washed with ether and the solids dissolved in 25 ml. water and acidified with hydrochloric acid and extracted several times with ether. The dried ether extracts were evaporated under reduced pressure yielding 0.9 g. (20.4%) of product, m.p. 126-128°C. α_D^{25} DMF -5.58°.

exo-2-(Benzilyloxy)-exo-3(N,N-dimethylaminomethyl)bicyclo[2.2.1]heptane Hydrochloride, ACC 7121-41

A mixture of 10.0 g. (0.059 mole) exo-2-hydroxy-exo-3(N,N-dimethylaminomethyl)bicyclo[2.2.1]heptane, 14.3 g. (0.059 mole) methyl benzilate and 200 ml. n-heptane was heated in the presence of freshly prepared sodium methoxide until the separation of methanol in a Dean-Stark separator ceased (0.9 ml. of theory of 3.0 ml.). Upon cooling the reaction mixture was filtered and washed with water until the washes were neutral. The organic fraction was extracted with dilute hydrochloric acid where a copious white precipitate formed. The solids were collected by filtration and recrystallized from 90 ml. isopropanol yielding 5.2 g. (21.2%) of product, m.p. 198-200°C.

Anal. Calcd. for $C_{24}H_{30}ClNO_3$: C, 69.29; H, 7.27; O, 11.54. Found: C, 69.2; H, 7.3; O, 11.8.

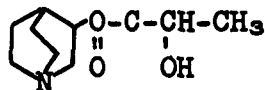
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DATA SHEET FOR COMPOUND NO. 7121-1
Lakeside Laboratories, Inc., Reference No. RB 1051-79B, EX 10-314

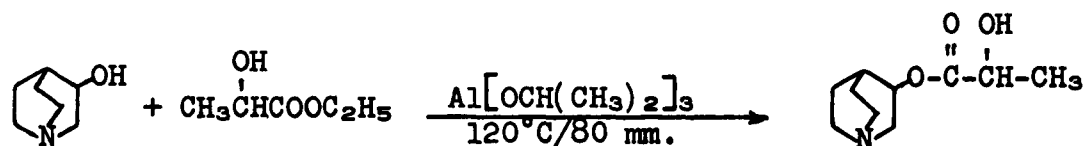
a. 3-Quinuclidyl Lactate



$C_{10}H_{17}NO_3$
 M.P. 73-76° (Corrected)
 M.W. 199.244

Amount: 1.0 g.

b. Synthetic Route



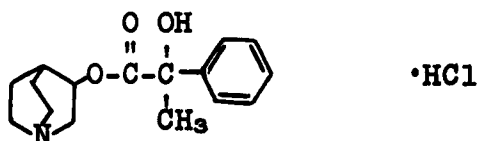
Ethyl lactate was allowed to react with 3-quinuclidinol in refluxing dry toluene in the presence of aluminum isopropoxide for three hours, and for one additional hour at the same temperature under 80 mm. pressure. The resulting ester was purified by distillation.

- c. Purity was determined by IR spectroscopy in these laboratories and by carbon and hydrogen analysis performed by Weiler-Strauss.
- d. Equipment utilized was conventional Pyrex standard taper laboratory glassware.

smr

Data Sheet for Compound No. 7121-4
Lakeside Laboratories, Inc., Reference No. RB 1051-95A, EX 10-324

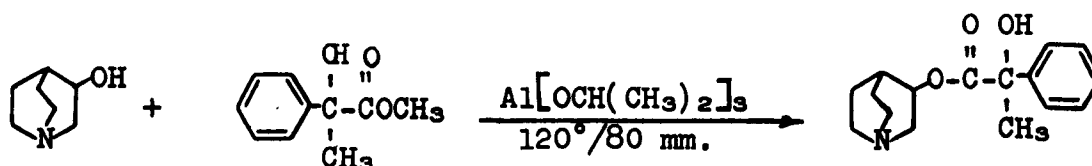
a. 3-Quinuclidyl atrolactate hydrochloride



$C_{16}H_{22}ClNO_3$
 M.P. 244-245° (corrected)
 M.W. 311.801

Amount: 1.0 g.

b. Synthetic Route



Methyl atrolactate was allowed to react with 3-quinuclidinol in refluxing dry toluene in the presence of aluminum isopropoxide for two hours, and for 1.5 additional hours at the same temperature under 80 mm. pressure. The resulting ester was converted to the hydrochloride salt and purified by recrystallization from acetonitrile.

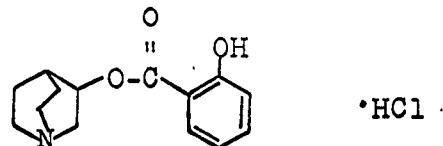
c. Purity was determined by IR spectroscopy performed in these laboratories and by carbon and hydrogen analysis performed at the United States Army Chemical Center.

d. Equipment utilized was conventional Pyrex standard taper laboratory glassware.

smr

DATA SHEET FOR COMPOUND NO. 7121-5
Lakeside Laboratories, Inc. Reference No. RB 1029-89C EX 10-200

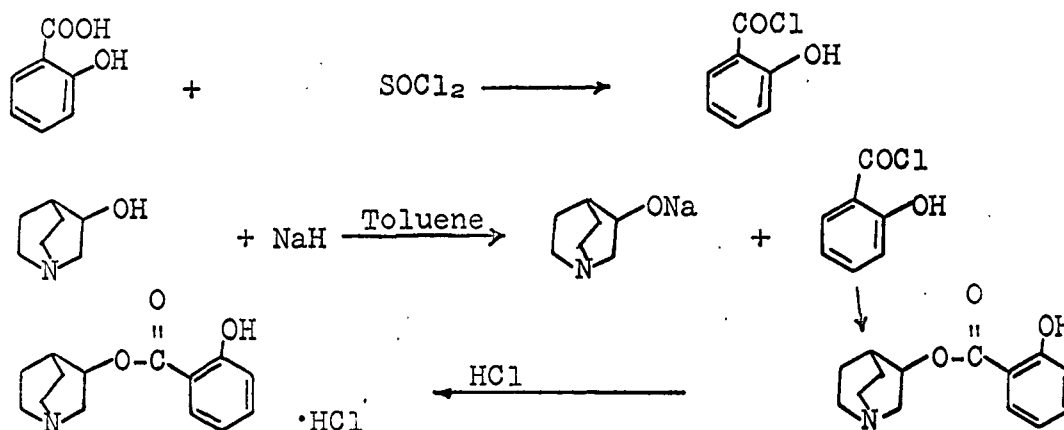
a. 3-Quinuclidyl-o-hydroxybenzoate Hydrochloride



$C_{14}H_{18}ClNO_3$
 M.W. 283.749
 M.P. 266-267° (d) corrected

Amount: 3 grams

b. Synthetic Route



o-Hydroxybenzoyl chloride was prepared as in U.S. 2,899,458. This chloride was reacted with the sodium anion of 3-quinuclidinol, the basic ester converted to the hydrochloride salt in ether and recrystallized twice from ethanol.

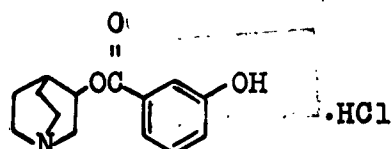
c. Purity was determined by IR spectroscopy and carbon, hydrogen and oxygen analysis performed at the United States Army Chemical Center.

d. Equipment utilized was conventional pyrex standard taper laboratory glassware.

1-7-63

DATA SHEET FOR COMPOUND NO. 7121-6
Lakeside Laboratories, Inc., Reference No. RB 1029-205A, EX 10-245

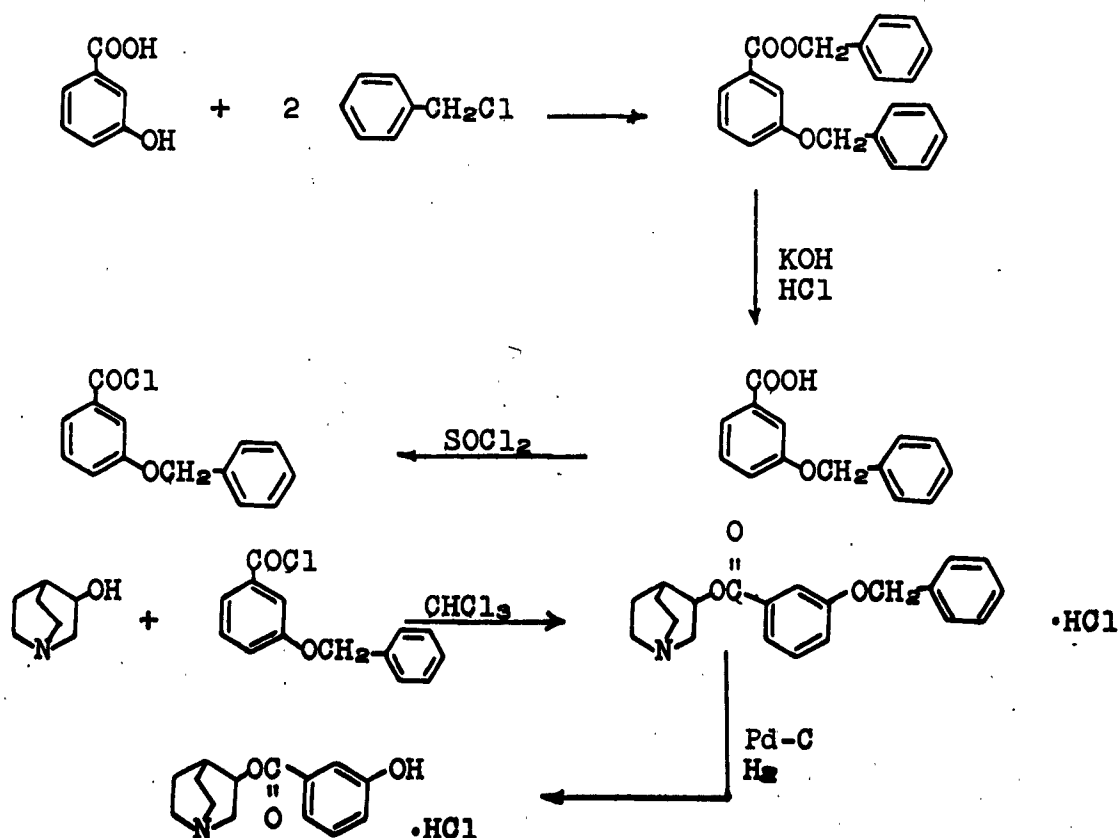
a. 3-Quinuclidyl-m-hydroxybenzoate Hydrochloride



$C_{14}H_{18}ClNO_3$
 M.W. 283.749
 M.P. 245-247°C (Corrected)

Amount: 3.0 g.

b. Synthetic Route



Benzyl-3-(benzyloxy)benzoate, 3-(benzyloxy)benzoic acid and 3-(benzyloxy)benzoyl chloride were prepared by the methods reported by Cavallito and Buck, J. Am. Chem. Soc. 65: 2140 (1943) for the 2- and 4- position isomers.

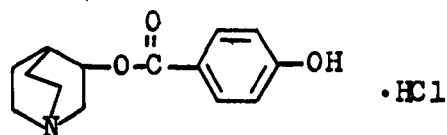
3(Benzyloxy)benzoyl chloride was allowed to react with 3-quinuclidinol in refluxing chloroform, and the crude m-benzyloxy ester isolated as the hydrochloride salt. The crude ester salt thus obtained was debenzylated in aqueous methanol at four atmospheres of hydrogen in the presence of palladium on carbon catalyst and the resulting product recrystallized from ethanol.

- c. Purity was determined by IR spectroscopy, nitrogen and chloride determinations in these laboratories and by carbon and hydrogen analysis performed at the United States Army Chemical Center.
- d. Equipment utilized was conventional Pyrex standard taper laboratory glassware and a Parr low pressure hydrogenation apparatus.

smr

DATA SHEET FOR COMPOUND NO. 7121-7
Lakeside Laboratories, Inc. Reference No. RB 1029-149A EX 10-220

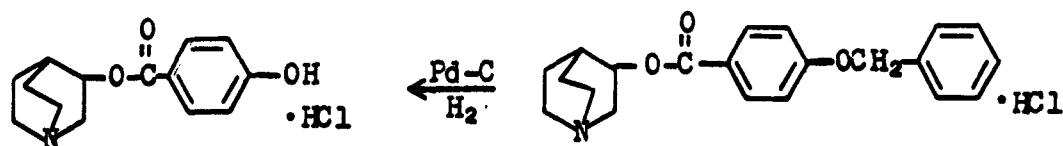
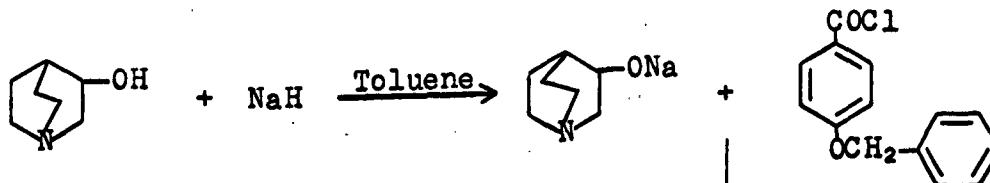
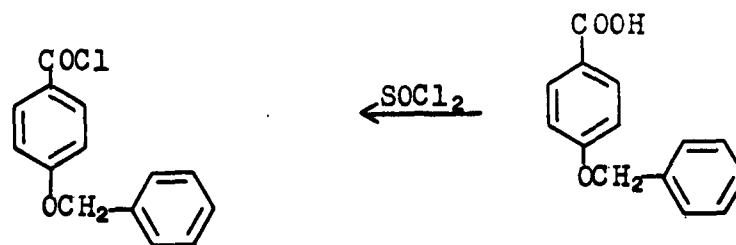
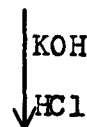
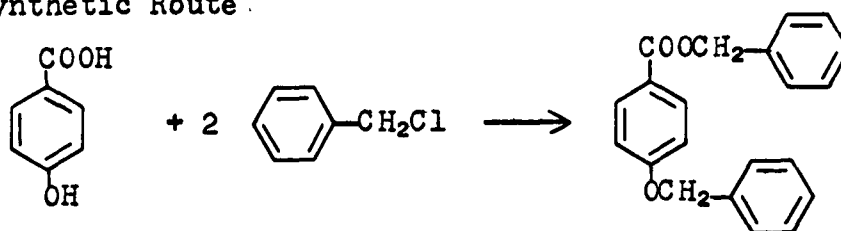
a. 3-Quinuclidyl-p-hydroxybenzoate Hydrochloride



$C_{14}H_{18}ClNO_3$
 M.W. 283.149
 M.P. 259-261° (corrected)

Amount: 1.0 gram

b. Synthetic Route



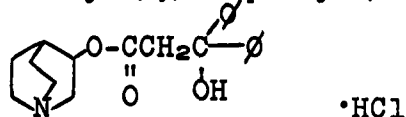
Benzyl-4(benzyloxy)benzoate, 4-(benzyloxy)benzoic acid and 4-(benzyloxy)benzoyl chloride were prepared as reported by Cavallito and Buck, J.A.C.S. 65: 2140 (1943).

4(Benzyloxy)benzoyl chloride was allowed to react with the sodium anion of 3-quinuclidinol, the basic ester converted to the hydrochloride salt in ether and recrystallized from isopropanol. The p-benzyloxy ester hydrochloride thus obtained was debenzylated in aqueous methanol at four atmospheres of hydrogen in the presence of palladium on carbon catalyst and the resulting product recrystallized from isopropanol.

- c. Purity was determined by IR spectroscopy and carbon, hydrogen and oxygen analysis performed at the United States Army Chemical Center.
- d. Equipment utilized was conventional pyrex standard taper laboratory glassware and a Parr low pressure hydrogenation apparatus.

DATA SHEET FOR COMPOUND NO. 7121-8

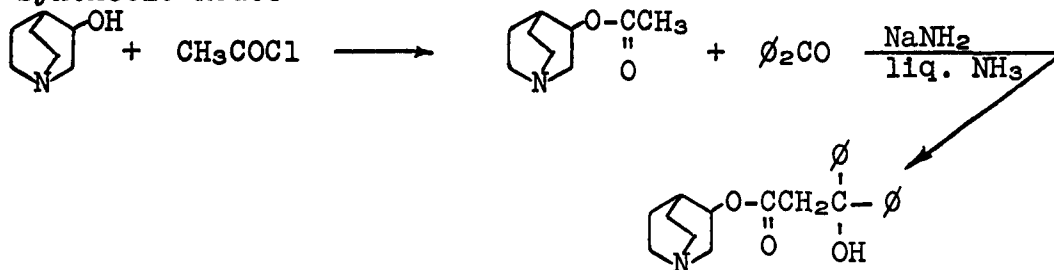
Lakeside Laboratories, Inc., Reference No. RB 1030-245, EX 10-304

a. 3-Quinuclidyl- β,β -diphenyl- β -hydroxypropionate hydrochloride

$C_{22}H_{26}ClNO_3$
 M.P. 243°C (corrected)
 M.W. 387.90

Amount: 1 g.

b. Synthetic Route



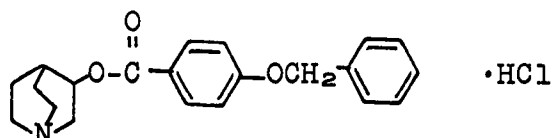
The 3-quinuclidinol was allowed to react with acetyl chloride in chloroform and the ester was purified by vacuum distillation. The 3-quinuclidyl acetate was allowed to react with benzophenone in liquid ammonia and sodium amide according to the procedure described by C. Hauser, J.O.C. 25; 1296-1302 (1960). The hydrochloride salt prepared from the above ester was purified by recrystallization from ethanol.

- c. Purity was determined by IR spectroscopy in these laboratories and by carbon and hydrogen assay performed at the United States Army Chemical Center.
- d. Equipment utilized was conventional pyrex standard taper laboratory glassware.

1-7-63

DATA SHEET FOR COMPOUND NO. 7121-9
Lakeside Laboratories, Inc. Reference No. RB 1029-205B, EX 10-246

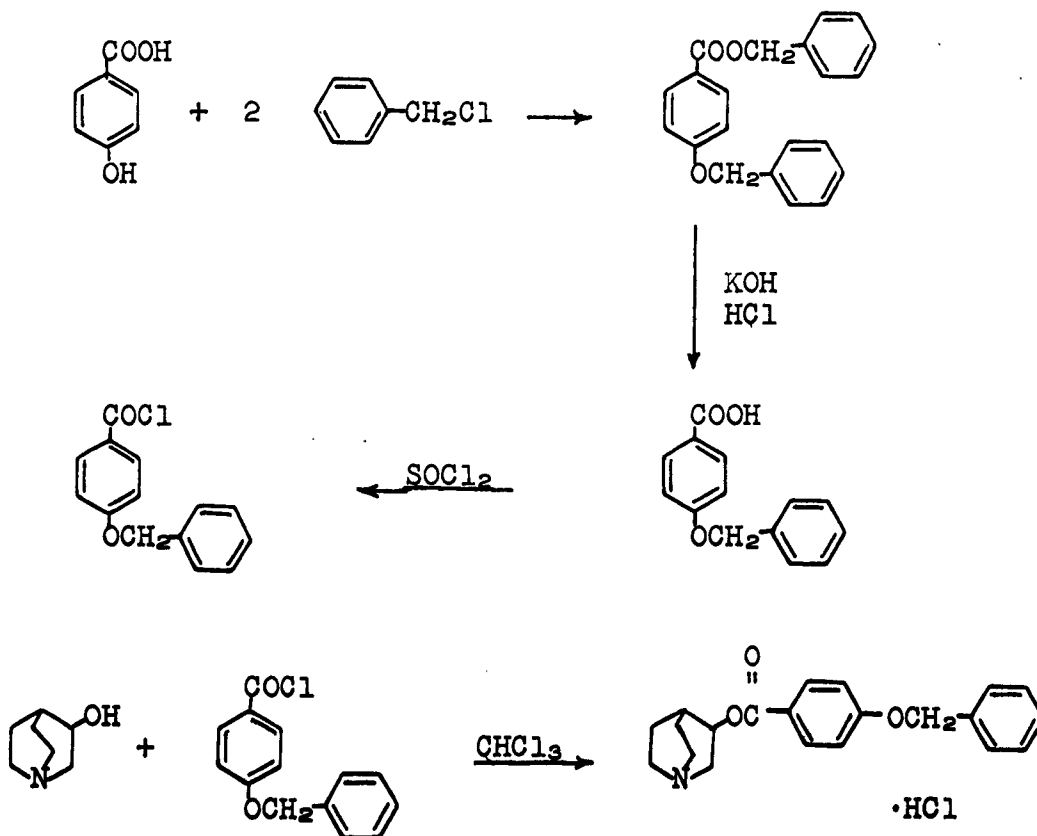
a. 3-Quinuclidyl-p-benzyloxybenzoate Hydrochloride



$C_{21}H_{24}ClNO_3$
 M.W. 373.867
 M.P. 236-237°C (Corrected)

Amount: 2.5 g.

b. Synthetic Route



Benzyl-4(benzyloxy)benzoate, 4-(benzyloxy)benzoic acid and 4-(benzyloxy)benzoyl chloride were prepared as reported by Cavallito and Buck, J. Am. Chem. Soc., 65: 2140 (1943).

4-(Benzyloxy)benzoyl chloride was allowed to react with 3-quinuclidinol in refluxing chloroform, the p-benzyloxy ester being isolated as the hydrochloride salt and purified by recrystallization from isopropanol.

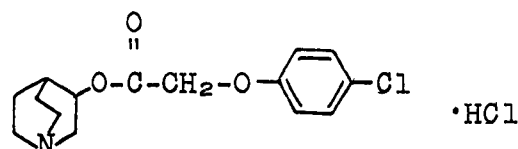
- c. Purity was determined by IR spectroscopy, nitrogen and chloride determinations in these laboratories and by carbon and hydrogen analysis performed at the United States Army Chemical Center.
- d. Equipment utilized was conventional Pyrex standard taper laboratory glassware.

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1-7-63

DATA SHEET FOR COMPOUND NO. 7121-10
Lakeside Laboratories, Inc. Reference No. RB 1029-205C, EX 10-247

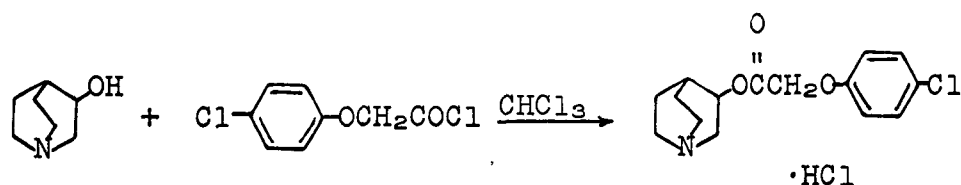
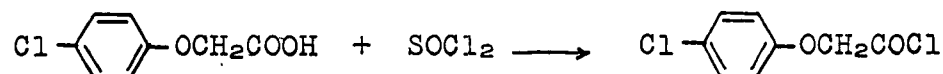
a. 3-Quinuclidyl-p-chlorophenoxyacetate Hydrochloride



$C_{15}H_{19}Cl_2NO_3$
M.W. 332.224
M.P. 199-201°C (Corrected)

Amount: 3.0 g.

b. Synthetic Route



p-Chlorophenoxyacetyl chloride was prepared as reported in Beil VI, Suppl. II, p. 177.

3-Quinuclidinol was allowed to react with p-chlorophenoxyacetyl chloride in refluxing chloroform and the resulting ester hydrochloride purified by recrystallization from isopropanol.

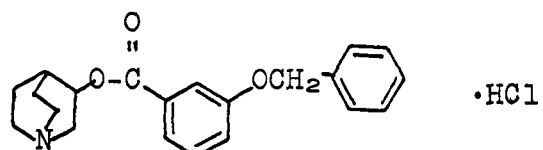
- c. Purity was determined by IR spectroscopy, nitrogen and chloride determinations in these laboratories and by carbon and hydrogen analysis performed at the United States Army Chemical Center.
- d. Equipment utilized was conventional Pyrex standard taper laboratory glassware.

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1-7-63

DATA SHEET FOR COMPOUND NO. 7121-11
Lakeside Laboratories, Inc., Reference No. RB 1029-205D, EX 10-248

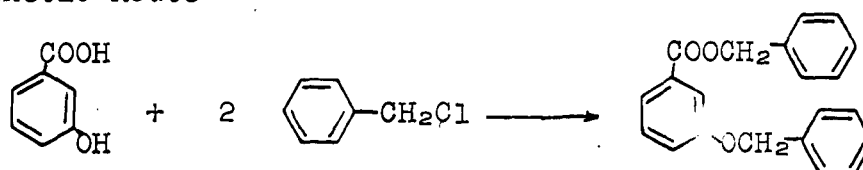
a. 3-Quinuclidyl-m-benzyloxybenzoate Hydrochloride



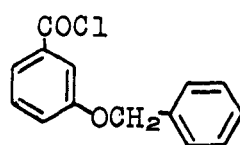
$C_{21}H_{24}ClNO_3$
 M.W. 373.867
 M.P. 186-188°C (Corrected)

Amount: 3.0 g.

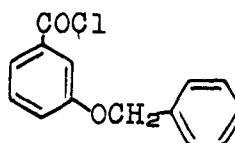
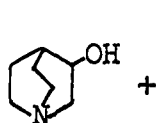
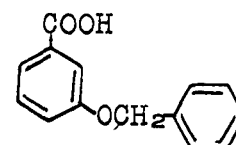
b. Synthetic Route



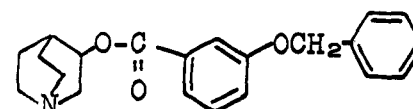
KOH
HCl



$SOCl_2$



$CHCl_3$



·HCl

Benzyl-3(benzyloxy)benzoate, 3-(benzyloxy)benzoic acid and 3-(benzyloxy)benzoyl chloride were prepared by the methods reported by Cavallito and Buck, J. Am. Chem. Soc. 65: 2140 (1943) for the 2- and 4- position isomers.

3-(Benzyloxy)benzoyl chloride was allowed to react with 3-quinuclidinol in refluxing chloroform, the m-benzyloxy ester being isolated as the hydrochloride salt and purified by recrystallization from isopropanol.

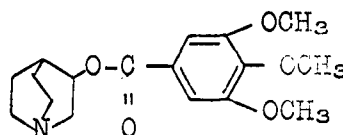
- c. Purity was determined by IR spectroscopy, nitrogen and chloride determinations in these laboratories and by carbon and hydrogen analysis performed at the United States Army Chemical Center.
- d. Equipment utilized was conventional Pyrex standard taper laboratory glassware.

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1-7-63

DATA SHEET FOR COMPOUND NO. 7121-12
Lakeside Laboratories, Inc., Reference No. RB 1029-205E, EX 10-249

a. 3-Quinuclidyl-3,4,5-trimethoxybenzoate Hydrochloride

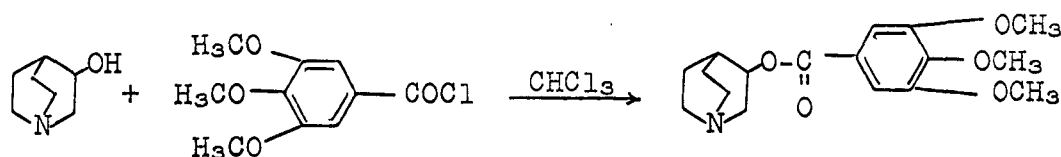
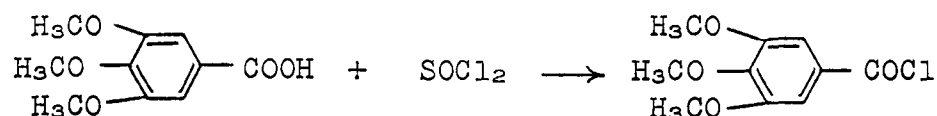


·HCl

$C_{17}H_{24}ClNO_5$
 M.W. 357.827
 M.P. 214-216°C (Corrected)

Amount: 3.0 g.

b. Synthetic Route



·HCl

3,4,5-Trimethoxybenzoyl chloride was prepared as reported by H. Rapoport, A. Williams and M. Cisney, J. Am. Chem. Soc., 73: 1414-21 (1951).

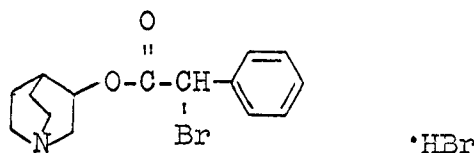
3,4,5-Trimethoxybenzoyl chloride was allowed to react with 3-quinuclidinol in refluxing chloroform and the resulting ester hydrochloride was purified by recrystallization from isopropanol.

- c. Purity was determined by IR spectroscopy, nitrogen and chloride analysis in these laboratories and by carbon and hydrogen analysis performed at the United States Army Chemical Center.
- d. Equipment utilized was conventional Pyrex standard taper laboratory glassware.

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DATA SHEET FOR COMPOUND NO. 7121-13
Lakeside Laboratories, Inc., Reference No. RB 1029-207A, EX 10-250

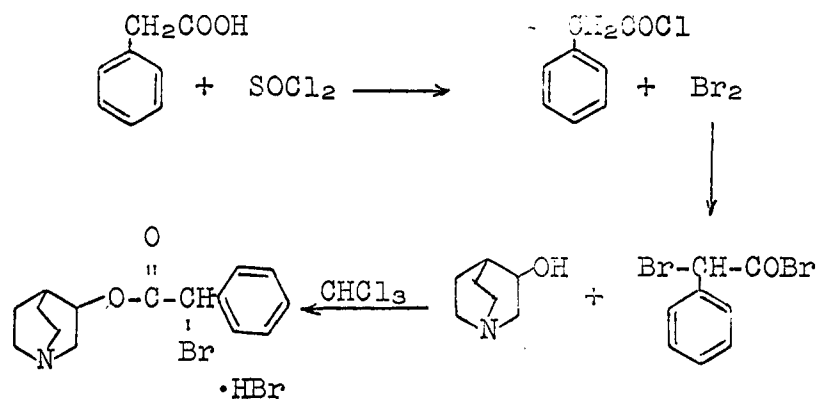
a. 3-Quinuclidyl- α -bromophenylacetate Hydrobromide



$C_{15}H_{19}Br_2NO$
 M.P. 183-185°C (Corrected)
 M.W. 405.142

Amount: 3.0 g.

b. Synthetic Route



Phenylacetyl chloride was prepared by reacting phenylacetic acid with thionyl chloride and distilling the product.
 (I.M. Heilbron, Dict. Org. Cpds. (1943), vol. 3, p. 376)

α -Bromophenylacetyl bromide was prepared as reported by Cohen, J. Chem. Soc., 99 1065.

3-Quinuclidinol was allowed to react with α -bromophenylacetyl bromide in refluxing chloroform and the resulting ester hydrochloride purified by recrystallization from acetonitrile.

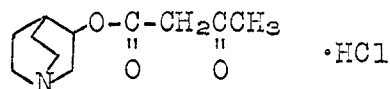
- c. Purity was determined by IR spectroscopy, nitrogen and chloride analysis in these laboratories and by carbon and hydrogen analysis performed by the United States Army Chemical Center.
- d. Equipment utilized was conventional Pyrex standard taper laboratory glassware.

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4-9-63

DATA SHEET FOR COMPOUND NO. 7121-14
Lakeside Laboratories, Inc., Reference No. RB 1030-241, EX 10-285

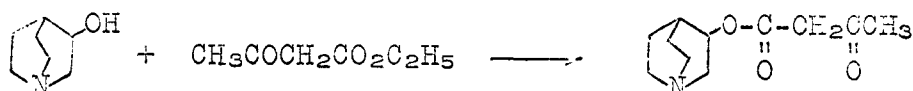
a. 3-Quinuclidyl acetoacetate hydrochloride



$C_{11}H_{18}ClNO_3$
M.P. 177-178°C (corrected)
M.W. 247.72

Amount: 1.0 g.

b. Synthetic Route



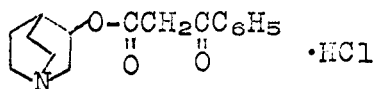
The 3-quinuclidinol was transesterified with ethyl acetoacetate according to the procedure reported by A. Bader, J. Amer. Chem. Soc., 73, 4195 (1951). The resulting ester hydrochloride was purified by recrystallization from ethyl acetate and ethanol (7-1).

- c. Purity was determined by IR spectroscopy in these laboratories and by carbon and hydrogen analysis performed by Weiler-Strauss.
- d. Equipment utilized was conventional pyrex standard taper laboratory glassware.

4-9-63

DATA SHEET FOR COMPOUND NO. 7121-15
Lakeside Laboratories, Inc., Reference No. RB 1030-243, EX 10-286

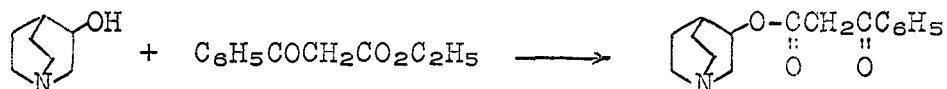
a. 3-Quinuclidyl Benzoylacetate hydrochloride



$C_{16}H_{20}ClNO_3$
M.P. 158-159°C (corrected)
M.W. 309.79

Amount: 1.0 g.

b. Synthetic Route



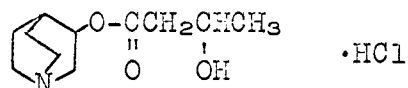
The 3-quinuclidinol was transesterified with ethyl benzoylacetate according to the procedure reported by A. Bader, J. Amer. Chem. Soc. 73, 4195 (1951). The resulting ester hydrochloride was purified by recrystallization from ethyl acetate and ethanol (2-1).

- c. Purity was determined by IR spectroscopy in these laboratories and by carbon and hydrogen analysis performed by Weiler-Strauss.
- d. Equipment utilized was conventional pyrex standard taper laboratory glassware.

4-12-63

DATA SHEET FOR COMPOUND NO. 7121-16
Lakeside Laboratories, Inc., Reference No. RB 1030-243A, EX 10-303

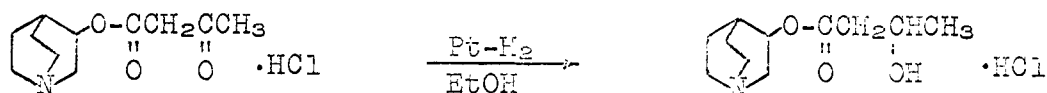
a. 3-Quinuclidyl-β-hydroxybutyrate Hydrochloride



$\text{C}_{11}\text{H}_{20}\text{ClNO}_3$
M.P. 155-156°C (corrected)
M.W. 249.74

Amount: 1 g.

b. Synthetic Route



The quinuclidyl acetoacetate ester was reduced in a Parr hydrogenator at 50°C under 60 psi hydrogen. The resulting ester hydrochloride was purified by recrystallization from isopropanol.

- c. Purity was determined by IR spectroscopy in these laboratories and by carbon and hydrogen analysis performed by Weiler-Strauss.
- d. Equipment utilized was conventional pyrex standard taper laboratory glassware.

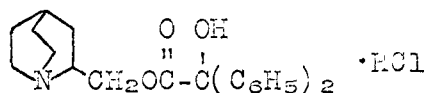
smr

CONFIDENTIAL

4-12-63

DATA SHEET FOR COMPOUND NO. 7121-17
Lakeside Laboratories, Inc., Reference No. RB 1051-51B, EX 10-305

a. 2-Quinuclidyl methylbenzilate hydrochloride



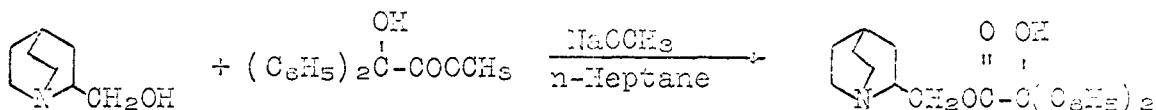
$C_{22}H_{28}ClNO_3$

M.P. 262°(d) (corrected)

M.W. 387.893

Amount: 1 g.

b. Synthetic Route



The 2-quinuclidyl methanol was transesterified with methyl benzilate in refluxing n-heptane in the presence of a freshly prepared solution of sodium in methanol as a catalyst. The ester was converted to the hydrochloride salt in ether and purified by recrystallization from acetonitrile.

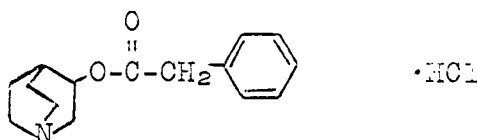
- c. Purity was determined by infrared spectroscopy, nitrogen and chloride analysis in these laboratories and by carbon-hydrogen analysis performed by Weiler-Strauss.
- d. Equipment utilized was conventional Pyrex standard taper laboratory glass ware.

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CONFIDENTIAL

DATA SHEET FOR COMPOUND NO. 7121-13
Lakeside Laboratories, Inc., Reference No. RB 1051-83A, EX 10-516

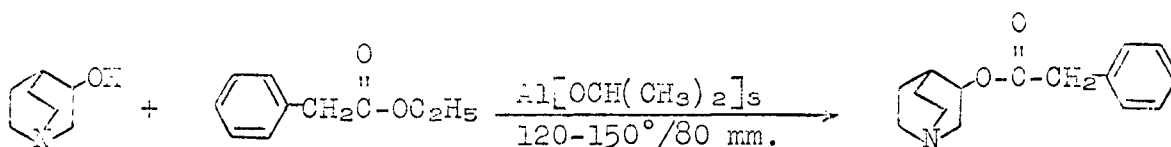
a. 3-Quinuclidyl phenylacetate hydrochloride



$C_{15}H_{20}ClNO_2$
 M.P. 180-181° (corrected)
 M.W. 281.775

Amount: 1.0 g.

b. Synthetic Route



Ethyl phenyl acetate was allowed to react with 3-quinuclidinol in the presence of aluminum isopropoxide under 80 mm. pressure for one hour at 120°C and for two hours additional at 150°C. The resulting ester was converted to its hydrochloride salt and purified by recrystallization from acetonitrile.

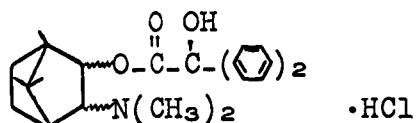
- c. Purity was determined by IR spectroscopy, nitrogen and chloride assays performed in these laboratories and by carbon and hydrogen analysis performed by Weiler and Strauss.
- d. Equipment utilized was conventional Pyrex standard taper laboratory glassware.

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6-27-63

DATA SHEET FOR COMPOUND NO. 7121-19
Lakeside Laboratories, Inc., Reference No. RB 1051-165A, EX 10-338

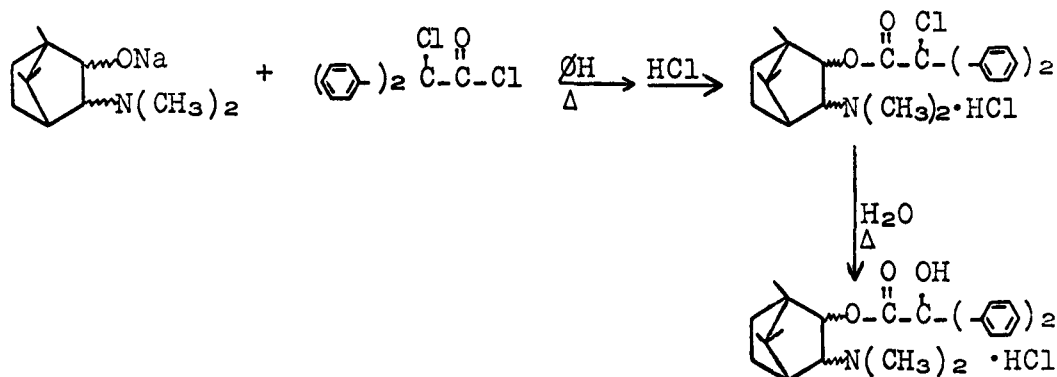
- a. 1,7,7-Trimethyl-2-benziloyloxy-3-N,N-dimethylamino-bicyclo-[2.2.1]-heptane hydrochloride



$C_{26}H_{34}ClNO_3$
 M.P. 294-296° (d) (corrected)
 M.W. 443.997

Amount: 1.0 g.

- b. Synthetic Route



α-Chlorodiphenylacetylchloride was allowed to react with the sodium anion of 3-N,N-dimethylamino borneol in refluxing benzene for three hours. The resulting α-chloro ester was converted to the hydrochloride salt which was then hydrolyzed to the appropriate α-hydroxy ester in boiling water and purified by recrystallization from acetonitrile and resuspension in boiling water.

- c. Purity was determined by nitrogen analysis and IR spectroscopy performed in these laboratories and by carbon and hydrogen analysis performed by Weiler and Strauss.
- d. Equipment utilized was conventional Pyrex standard taper laboratory glassware.

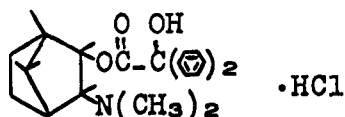
snb

CONFIDENTIAL

CONFIDENTIAL

Data Sheet for Compound No. 7121-20
Lakeside Laboratories, Inc., Reference No. RB 1051-233B EX 10-356

a. 1,7,7-Trimethyl-endo-2-benziloyloxy-endo-3-N,N-dimethylamino bicyclo-[2.2.1]-heptane hydrochloride



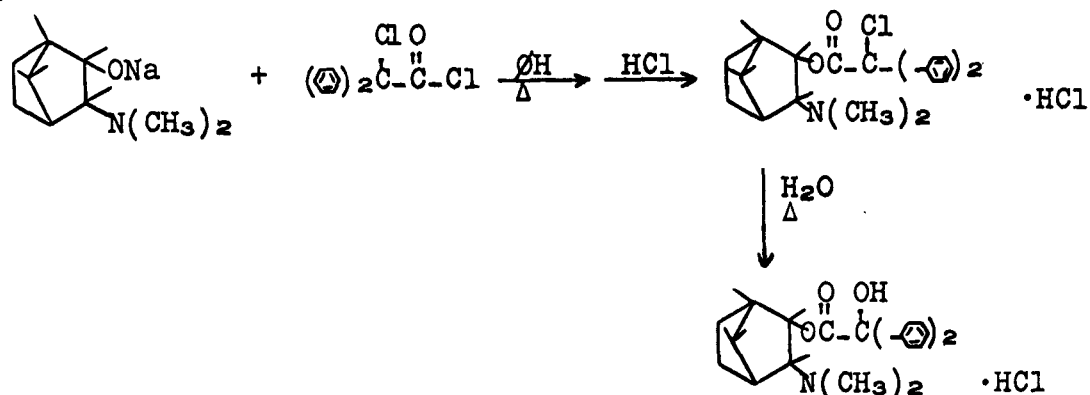
$C_{26}H_{34}ClNO_3$

Amount 1.0 gram

MW 443.997

MP 284-285°C (Corrected)

b. Synthetic route



α -Chlorodiphenyl acetyl chloride was allowed to react with the sodium anion of endo-3-N,N-dimethylamino borneol in refluxing benzene for three hours. The resulting α -chloro ester was converted to the hydrochloride salt which was then hydrolyzed to the appropriate α -hydroxy ester in boiling water and purified by recrystallization from acetonitrile.

c. Purity was determined by nitrogen analysis and IR spectroscopy performed in these laboratories and by carbon, hydrogen and oxygen analysis performed at the United States Army Chemical Center.

Analysis %N, 3.15, cal. Found %N, 3.17.

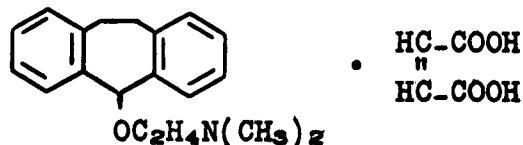
d. Equipment utilized was conventional Pyrex standard taper laboratory glassware.

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Data Sheet for Compound No. 7121-21
Lakeside Laboratories, Inc., Reference No. RB 1054-51, EX 10-346

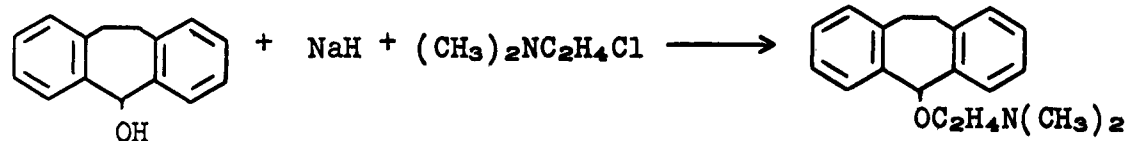
- a. 5-[β -(N,N-Dimethylamino)ethoxy]5-H-dibenzol[a,d]cycloheptadiene maleate



$\text{C}_{23}\text{H}_{27}\text{NO}_5$
 M.W. 397.46
 M.P. 121-122°

Amount: 1 gram

- b. Synthetic Route



The sodium alcoholate was prepared by refluxing the alcohol and sodium hydride in toluene. Freshly distilled β -dimethyl aminoethyl chloride was added to the anion solution and the mixture was refluxed for six hours. The base was converted to the maleate salt in ether and purified by recrystallization from ethyl acetate.

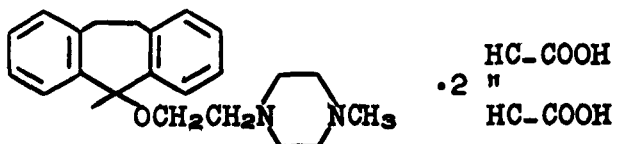
C. Van Der Stelt, A. F. Harms and W. Th. Nauta, J. Med. Pharm. Chem.,
 Volume 4(2) 335-349 (1961).

- c. Purity was determined by infrared spectroscopy, nitrogen and neutral equivalent analysis in these laboratories.
- d. Equipment utilized was conventional Pyrex standard taper laboratory glassware.

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Data Sheet for Compound No. 7121-22
Lakeside Laboratories, Inc., Reference No. RB 1051-231A, EX 10-354

a. 5-[β -(4-Methyl-1-piperazinyl)ethoxy]-5H-dibenzo[a,d]
cycloheptadiene bis maleate



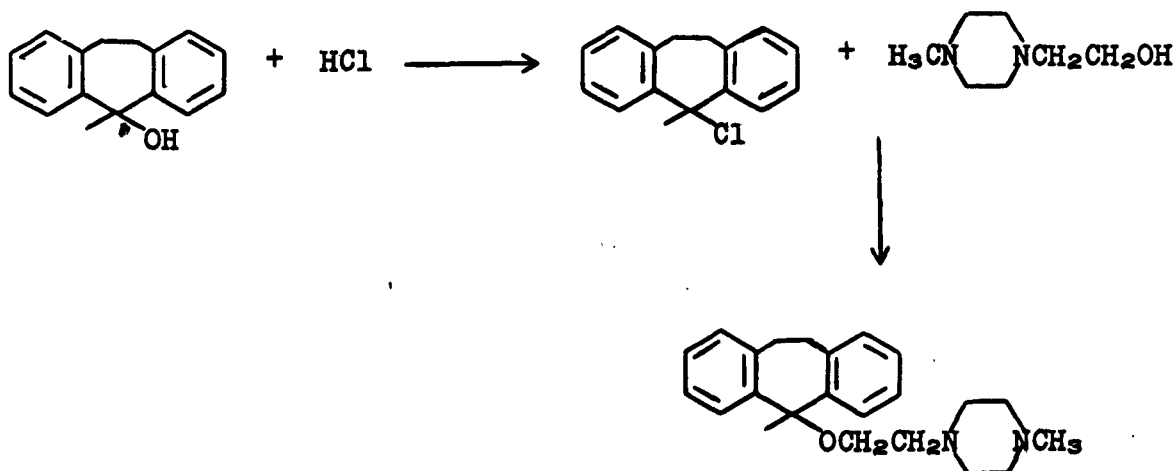
$C_{30}H_{36}N_2O_8$

Amount 1.0 gram

MW 568.604

MP 174-175°

b. Synthetic Route



Anhydrous hydrogen chloride was bubbled through a cooled benzene solution of the alcohol and the resulting chloro compound was added to a solution of 1-methyl-4-piperazinyl ethanol in xylene and the mixture was refluxed for three hours. The base was converted to the bis maleate salt in ethanol-ether and recrystallized from ethanol-ethylacetate.

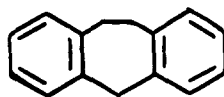
- c. Purity was determined by carbon and hydrogen assay performed by Weiler and Strauss.

Assay Calc. %C, 63.36, %H, 6.38. Found: %C, 63.12, %H, 6.26.

- d. Equipment utilized was conventional Pyrex standard taper laboratory glassware.

Data Sheet for Compound No. 7121-23
Lakeside Laboratories, Inc., Reference No. RB 1051-233A, EX 10-355

a. N-(2-N,N-Dimethylaminoethyl)-10,11-dihydro-5H-dibenzo[a,d]
cyclohepten-5-amine dihydrochloride



•2HCl

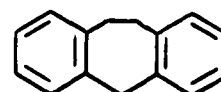
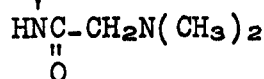
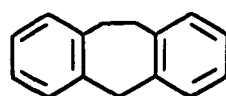
C₁₉H₂₆Cl₂N₂

Amount 1.0 gram

MW 353.328

MP 185-187°C

b. Synthetic route



The amide was reduced with aluminum chloride-lithium aluminum hydride in anhydrous ether and the base converted to the dihydrochloride salt in ether and was purified by recrystallization from ethanol-ethyl ether.

U. S. 3,052,721 Example 14

c. Purity was determined by nitrogen, chloride assay and IR spectroscopy in these laboratories and by carbon-hydrogen analysis by Weiler and Strauss.

Assay calc. %C, 64.59; %H, 7.41; %N, 7.93; Cl, 20.07.

Found: %C, 64.40; %H, 7.22; %N, 7.84; %Cl, 20.26.

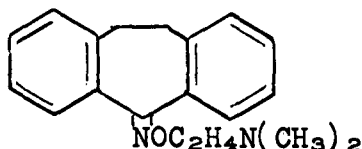
d. Equipment utilized was conventional Pyrex standard taper laboratory glassware.

snb

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Data Sheet for Compound No. 7121-24
Lakeside Laboratories, Inc., Reference No. RB 1054-103A, EX 10-367

- a. o-[β -(N,N-Dimethylamino)ethyl]10,11-Dihydro Dibenzo [a,d]
 Cyclohepten-5-one Oxime Fumarate



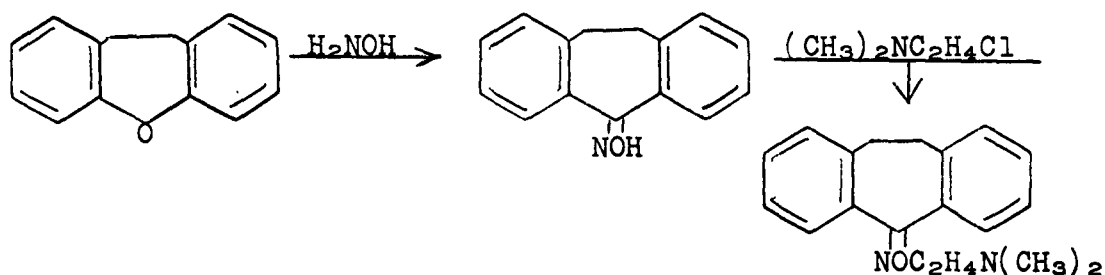
$\text{C}_{23}\text{H}_{26}\text{N}_2\text{O}_5$

Amount: 1 gram

MW 410.46

MP 140-142

- b. Synthetic route:



The oxime was prepared according to the procedure reported by A. M. Monro, R. M. Quinton and T. J. Wrigley, J. Med. Chem., Volume 6, No. 3, p. 255-261 (1963). The oxime was alkylated using sodium hydride and dimethylaminoethyl chloride in benzene. The resulting fumarate salt was purified by recrystallization from ethanol.

- c. Purity was determined by nitrogen assay and U.V. and I.R. spectroscopy in these laboratories and by carbon-hydrogen analysis by Weiler and Strauss.

Assay Calc. %C, 67.30; %H, 6.38; %N, 6.82
 Found: %C, 67.49; %H, 6.54; %N, 6.82

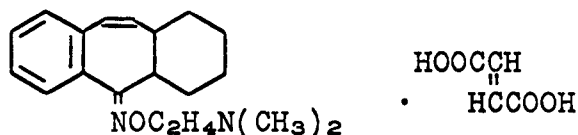
- d. Equipment utilized was conventional Pyrex standard taper laboratory glassware.

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Data Sheet for Compound No. 7121-25
Lakeside Laboratories, Inc., Reference No. RB 1054-103B, EX 10-368

- a. o-[β -(N,N-Dimethylamino)ethyl]dibenzo[a,d]cyclohepten-5-one oxime fumarate



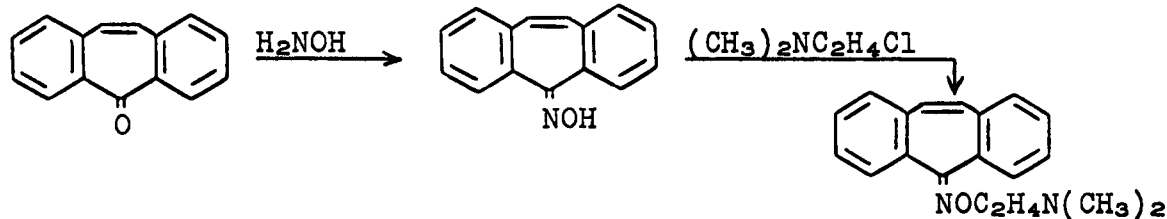
$C_{23}H_{24}N_2O_5$

Amount: 1 gram

MW 408.45

MP 159-160°

- b. Synthetic route:



The oxime was prepared according to the procedure reported by A. M. Monro, R. M. Quinton and T. J. Wrigley, J. Med. Chem., Volume 6, No. 3, p. 255-261 (1963). The oxime was alkylated using sodium hydride, and dimethylaminoethyl chloride in benzene. The resulting fumarate salt was purified by recrystallization from ethanol.

- c. Purity was determined by nitrogen assay and U.V. and I.R. spectroscopy in these laboratories and by carbon-hydrogen analysis by Weiler and Strauss.

Assay Calc. %C, 67.63; %H, 5.92; %N, 6.86
Found: %C, 67.51; %H, 5.99; %N, 6.87.

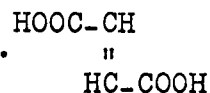
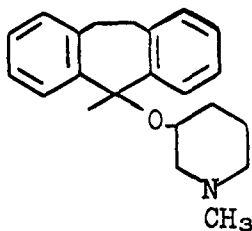
- d. Equipment utilized was conventional Pyrex standard taper laboratory glassware.

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Data Sheet for Compound No. 7121-26
Lakeside Laboratories, Inc., Reference No. RB 1051-283E, EX 10-370

a. 5-(1-Methyl-3-piperidyloxy)-5H-dibenzo[a,d]cycloheptadiene
acid fumarate



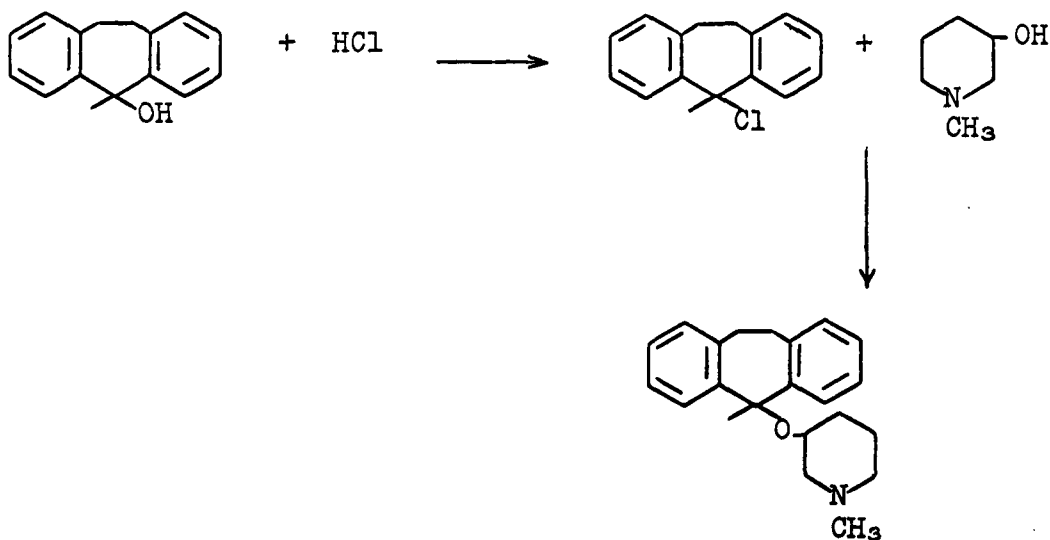
$\text{C}_{25}\text{H}_{29}\text{NO}_5$

Amount: 1.0 gram

MW 423.52

MP 167-168° (d) corrected

b. Synthetic route:



Anhydrous hydrogen chloride was bubbled through a cooled benzene solution of the alcohol. The resulting chloro-

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Data Sheet, Compound 7121-26
Lakeside Laboratories, Inc.
October 14, 1963
Page 2

compound was added to a solution of 1-methyl-3-hydroxy piperidine in toluene, and the mixture was refluxed for six hours. The base was purified by distillation and was converted to the acid fumarate salt in ether-ethanol which was recrystallized from ethanol.

- c. Purity was determined by IR spectroscopy and nitrogen and Neutral Equivalent analysis in these laboratories and by carbon and hydrogen assay performed by Weiler and Strauss.

Assay Calcd.: C, 70.90; H, 6.90; N, 3.31; N.E., 211.7.
Found: C, 70.88; H, 7.00; N, 3.35; N.E., 209.5.

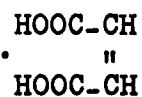
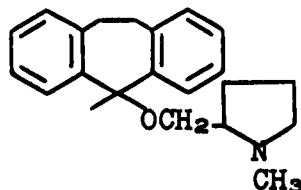
- d. Equipment utilized was conventional Pyrex standard taper laboratory glassware.

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Data Sheet for Compound No. 7121-27
Lakeside Laboratories, Inc., Reference No. RB 1051-283F, EX 10-371

a. 5-(1-Methyl-2-pyrrolidylmethoxy)-5H-dibenzo[a,d]cycloheptadiene
acid maleate



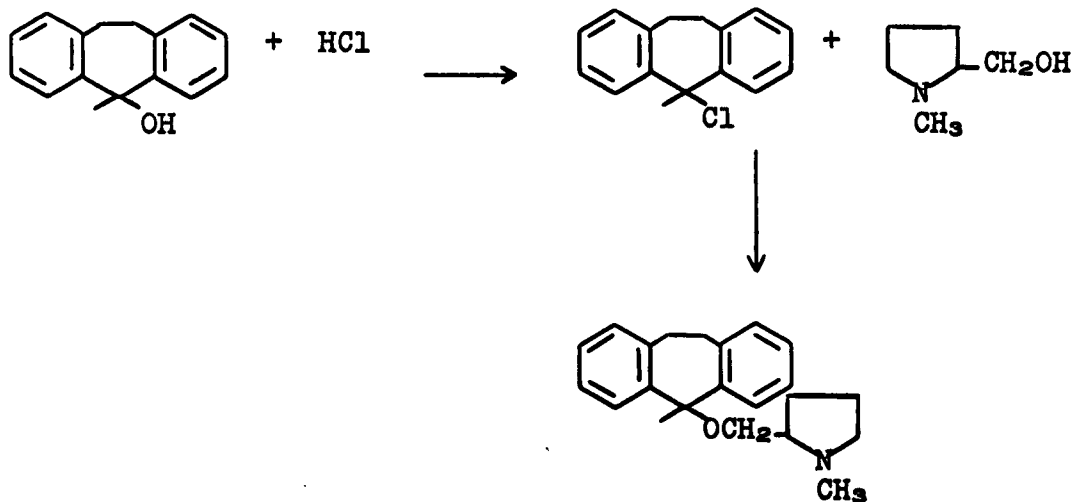
$C_{25}H_{29}NO_5$

Amount: 1.0 gram

MW 423.52

MP 109-110° (corrected)

b. Synthetic route:



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Anhydrous hydrogen chloride was bubbled through a benzene solution of the alcohol. The resulting chloro-compound was added to a solution of 1-methyl-2-pyrrolidyl methanol in toluene, and the mixture refluxed for six hours. The base was purified by distillation, was converted to the acid maleate salt in anhydrous ethyl ether which was recrystallized from ethyl acetate-ethyl ether.

- c. Purity was determined by IR spectroscopy and nitrogen and neutral equivalent analysis in these laboratories and by carbon and hydrogen assay performed by Weiler and Strauss.

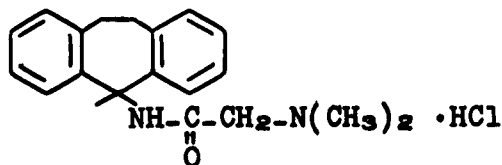
Assay Calcd.: C, 70.90; H, 6.90; N, 3.31; NE, 211.7.
Found: C, 70.89; H, 7.11; N, 3.23; NE, 221.9.

- d. Equipment utilized was conventional Pyrex standard taper laboratory glassware.

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Data Sheet for Compound No. 7121-28
Lakeside Laboratories, Inc., Reference No. RB 1076-19, EX 10-382

- a. N(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-2-N,N-Dimethyl-
 aminoacetamide hydrochloride



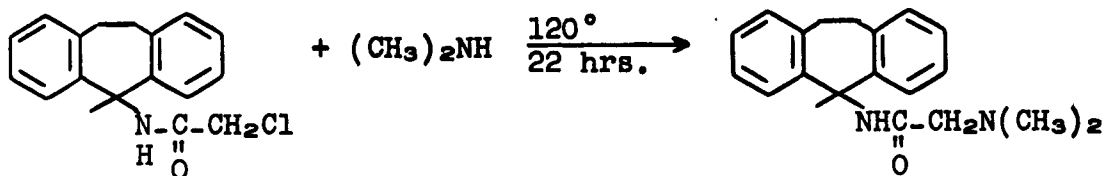
$C_{18}H_{23}ClN_2O$

Amount 1.0 g.

MW 330.847

MP 208° (d) corrected

- b. Synthetic route:



A mixture of 2-chloro-N-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)acetamide and excess alcoholic dimethylamine was heated in an autoclave at 120°C for 22 hours. Upon cooling the solvents were removed by evaporation and crystallized under ether, collected by filtration and washed well with water. The resulting amide was purified by recrystallization from ethanol and then converted to the hydrochloride salt in ethanol.

Bernstein and Losee, U. S. 3,052,721.

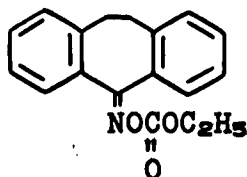
- c. Purity was determined by IR spectroscopy, nitrogen and chlorine analysis in these laboratories and by carbon and hydrogen assay performed by Weiler and Strauss.

Anal. Calcd.: C, 68.98; H, 7.01; N, 8.47; Cl, 10.72.
 Found: C, 68.94; H, 7.18; N, 8.71; Cl, 10.79.

- d. Equipment utilized was conventional Pyrex standard taper laboratory glassware.

Data Sheet for Compound No. 7121-29
Lakeside Laboratories, Inc., Reference No. RB 1076-23A, EX 10-361

a. O-Carboethoxy-10,11-dihydrodibenzo[a,d]cyclohepten-5-one oxime



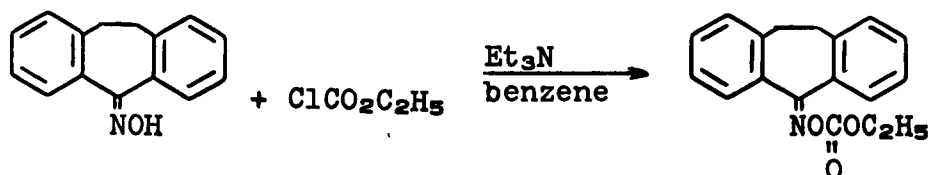
C₁₈H₁₇NO₃

Amount 1.0 Gram

M.W. 295.33

M.P. 112-113°

b. Synthetic route:



Dibenzo[a,d]cycloheptadiene-5-one oxime was allowed to react with ethylchloroformate in refluxing benzene in the presence of triethylamine. The product was purified by trituration under Skelly B.

- c. Purity was determined by IR spectroscopy in these laboratories and by carbon and hydrogen assay by Weller and Strauss.

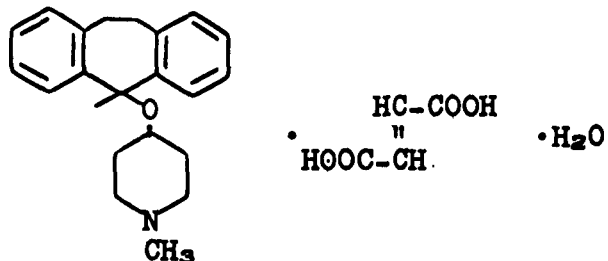
Anal. Calcd. for C₁₈H₁₇NO₃: C, 73.20; H, 5.80. Found: C, 73.48; H, 5.74.

- d. Equipment utilized was conventional Pyrex standard taper laboratory glassware.

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Data Sheet for Compound No. 7121-30
Lakeside Laboratories, Inc., Reference No. RB 1076-135B, EX 10-426

a. 5-(1-Methyl-4-piperidyloxy)-5H-dibenzo-[a,d]-cycloheptadiene Acid Fumarate Monohydrate



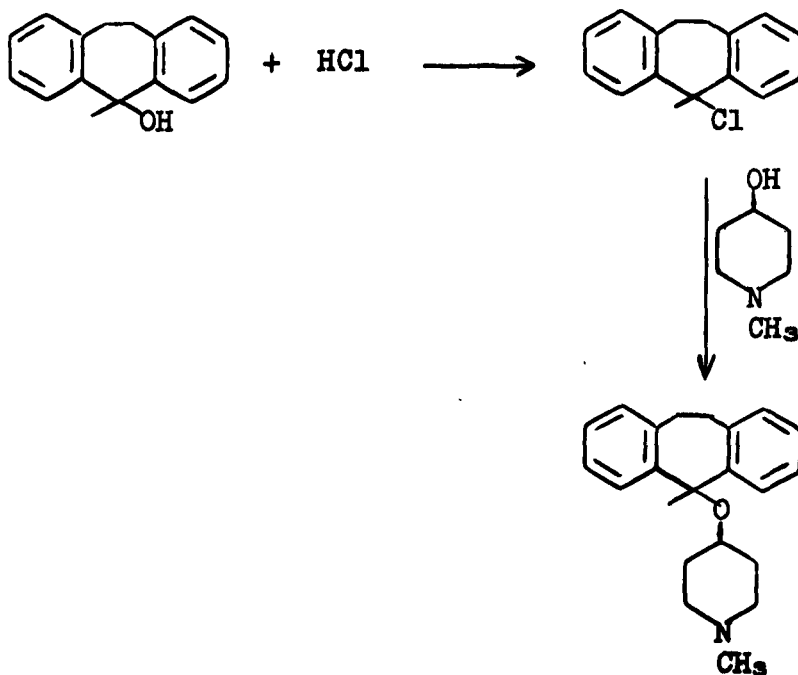
$\text{C}_{25}\text{H}_{31}\text{NO}_6$

Amount 1.0 Gram

M.W. 441.506

M.P. 163-164° (corrected)

b. Synthetic route:



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Anhydrous hydrogen chloride was bubbled through a cooled benzene solution of the alcohol. The resulting chloro-compound was added to a solution of 1-methyl-4-hydroxypiperidine in toluene, and the mixture was refluxed for six hours. The base was purified by distillation and was converted to the acid fumarate salt in ether-tetrahydrofuran and recrystallized from acetonitrile.

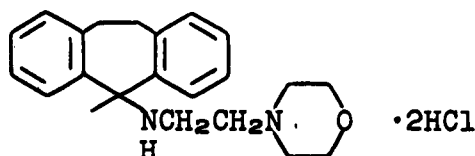
- c. Purity was determined by IR spectroscopy in these laboratories, by carbon and hydrogen assay performed by Weiler and Strauss and oxygen analysis performed by the U. S. Army Chemical Center.

Assay Calcd.: C, 68.01; H, 7.08; O, 21.75. Found: C, 68.00; H, 6.80; O, 21.2.

- d. Equipment utilized was conventional Pyrex standard taper laboratory glassware.

Data Sheet for Compound No. 7121-31
Lakeside Laboratories, Inc., Reference. No. RB 1076-109A, EX 10-414

a. 5-(4-Morpholinoethylamino)-10,11-dihydro-5H-dibenzo[a,d]cyclohepta-
diene Dihydrochloride



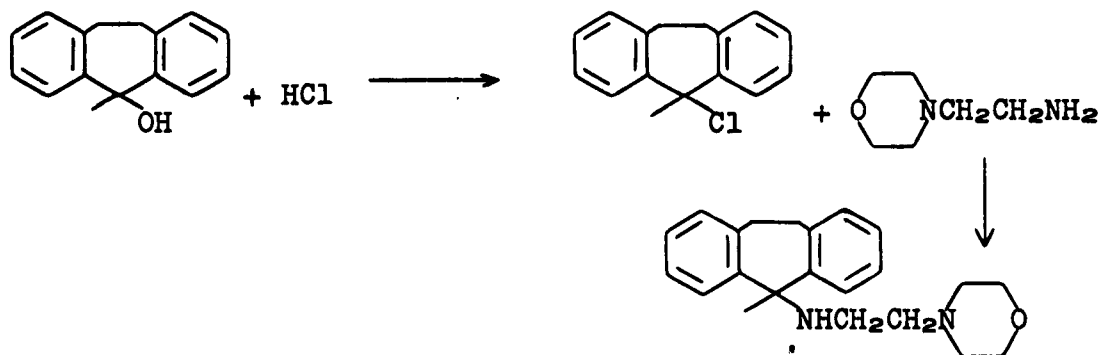
$C_{21}H_{28}Cl_2N_2O$

Amount 1.0 Gram

M.W. 395.364

M.P. 208-209° (corrected)

b. Synthetic route:



Anhydrous hydrogen chloride was bubbled through a cooled benzene solution of the alcohol and the resulting chloro compound was added to a solution of 4-morpholinoethylamine in toluene and the mixture was refluxed for six hours. The base was purified by distillation, converted to the hydrochloride salt in ether and purified by recrystallization from acetonitrile.

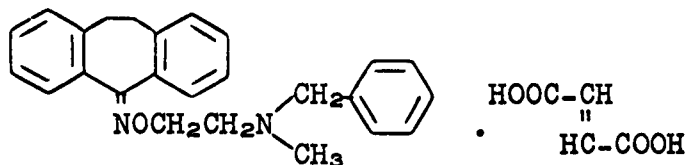
- c. Purity was determined by nitrogen and chloride assay and IR spectroscopy in these laboratories and by carbon and hydrogen analysis by Weiler and Strauss.

Anal. Calcd.: C, 63.79; H, 7.14; N, 7.08; Cl, 17.93.
Found: C, 63.65; H, 7.07; N, 6.92; Cl, 17.51.

- d. Equipment utilized was conventional Pyrex standard taper laboratory glassware.

Data Sheet for Compound No. 7121-32
Lakeside Laboratories, Inc., Reference No. RB 1076-135A, EX 10-424

a. O-[β -(N-Benzyl-N-methylamino)ethyl]-10,11-dihydro dibenzo-[a,d]-
 -cyclohepten-5-one Oxime Acid Fumarate



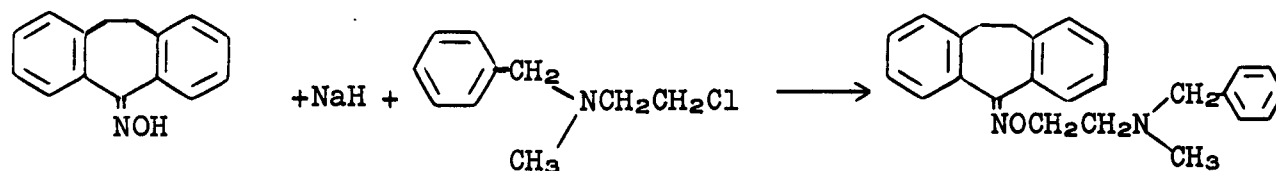
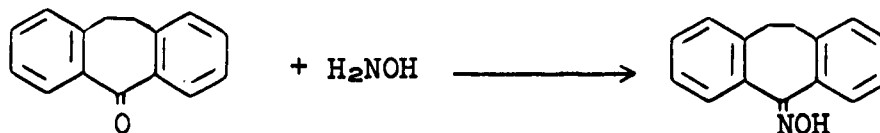
$C_{29}H_{30}N_2O_5$

Amount 1.0 Gram

M.W. 486.546

M.P. 149-150° (corrected)

b. Synthetic route:



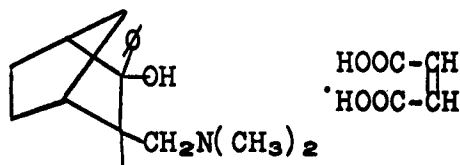
The oxime was prepared according to the procedure reported by A. M. Monro, R. M. Quinton and T. J. Wrigley; J. Med. Chem., Vol. 6, No. 3, p. 255-261 (1963). The oxime was alkylated using sodium hydride and N-benzyl-N-methylaminoethyl chloride in refluxing toluene. The resulting fumarate salt was recrystallized from isopropyl alcohol.

c. Purity was determined by infrared spectroscopy in these laboratories and carbon, hydrogen and nitrogen analysis by Weiler and Strauss.

Assay Calcd.: C, 71.58; H, 6.21; N, 5.75. Found: C, 71.56; H, 6.15; N, 5.49.

d. Equipment utilized was conventional Pyrex standard taper laboratory glassware.

a. endo-2-Hydroxy-2-phenyl-exo-3-(N,N-dimethylaminomethyl)-bicyclo[2,2,1]heptane Acid Maleate

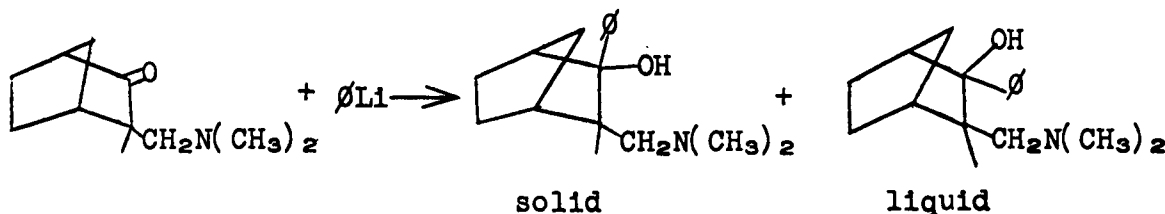


Amount 1.0 g.

M.W. 361.424

M.P. 191-193° (corrected)

b. Synthetic route:



3(N,N-dimethylaminomethyl)-bicyclo[2,2,1]heptanone-2 was allowed to react with phenyl lithium in ethyl ether. The reaction mixture was poured into ice water, washed with saturated sodium chloride, and the dried organic fraction evaporated under reduced pressure. The residues upon trituration with Skellysolve B afforded the solid isomer which was further purified by recrystallization from Skellysolve B. The maleate salt was prepared in ethyl ether and recrystallized from acetonitrile.

c. Purity was determined by infrared spectroscopy and gas chromatography performed in these laboratories and by carbon, hydrogen and nitrogen analysis performed by Weiler and Strauss. Configuration was determined by hydrogen bonding studies in the infrared.

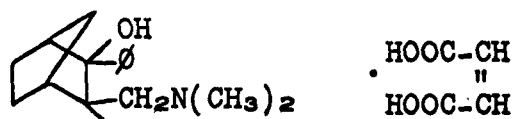
Anal. Calc. C, 66.47; H, 7.53; N, 3.88
Found: C, 66.29; H, 7.41; N, 3.94

d. Equipment utilized was conventional Pyrex standard taper laboratory glassware.

C

Data Sheet for Compound 7121-34
Lakeside Laboratories, Reference No. RB 1076159; EX 10-438

- a. exo-2-Hydroxy-2-phenyl-exo-3-(N,N-dimethylaminomethyl)-bicyclo-[2,2,1]heptane Acid Maleate



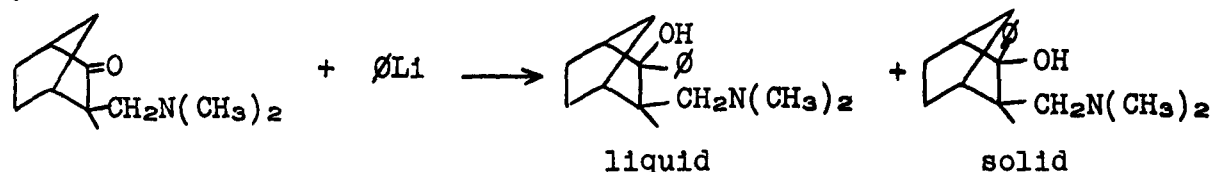
$C_{20}H_{27}NO_5$

Amount 1.0 g.

M.W. 361.424

M.P. 139-141° (corrected)

- b. Synthetic route:



3-(N,N-Dimethylaminomethyl)-bicyclo[2,2,1]heptanone-2 was allowed to react with phenyl lithium in ethyl ether. The reaction mixture was poured into ice-water, washed with saturated sodium chloride and the dried organic fraction evaporated under reduced pressure. These residues upon trituration in Skellysolve B afforded the solid isomer which could be further purified by recrystallization from Skellysolve B. Upon evaporation of the Skellysolve mother-liquors, a mixture of the liquid and solid isomers was obtained which could be purified by formation of the maleate salt and crystallization from acetonitrile which afforded only the salt of the solid isomer. Evaporation of the acetonitrile mother-liquors and recrystallization of the residues from ethyl acetate yielded the acid maleate salt of the liquid (cis) isomer.

- c. Purity was determined by infrared spectroscopy and gas chromatography in these laboratories and by carbon, hydrogen and nitrogen analysis performed by Weiler and Strauss.

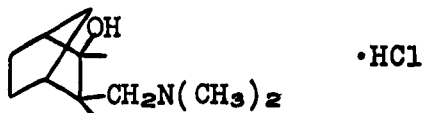
Anal. Calcd. for C, 66.47; H, 7.53; N, 3.88.
Found: C, 66.18; H, 7.50; N, 3.62.

Configuration was determined by hydrogen bonding studies in the infrared.

- d. Equipment utilized was conventional Pyrex standard taper laboratory glassware.

Data Sheet for Compound 7121-35
Lakeside Laboratories, Reference No. RB 1078-45A; EX 10-439

- a. exo-2-Hydroxy-exo-3-(N,N-dimethylaminomethyl)-bicyclo[2,2,1]-heptane Hydrochloride



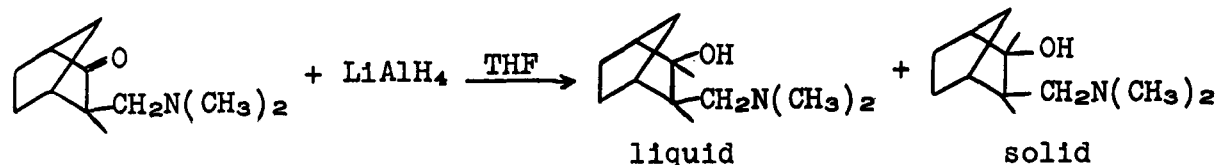
C₁₀H₂₀ClNO

Amount 1.0 g.

M.W. 205.73

M.P. 218-219° (corrected)

- b. Synthetic route:



3-(N,N-Dimethylaminomethyl)-bicyclo[2,2,1]heptanone-2 was reduced with lithium aluminum hydride in refluxing tetrahydrofuran. The isomeric forms of the alcohol were separated by fractional distillation through a Stedmann column. The hydrochloride salt was prepared in ethyl ether and recrystallized from ethanol.

- c. Purity was determined by infrared spectroscopy in these laboratories and by carbon and hydrogen analysis performed by Weiler and Strauss.

Configuration was determined by hydrogen-bonding studies in the infrared.

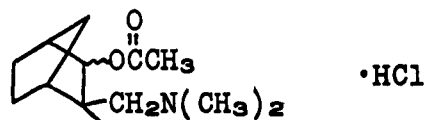
Anal. Calcd. for C, 58.38; H, 9.80.

Found: C, 58.43; H, 9.93.

- d. Equipment utilized was conventional Pyrex standard taper laboratory glassware.

Data Sheet for Compound 7121-36
Lakeside Laboratories, Reference No. RB 1078-47; EX 10-440

- a. (mixture of endo and exo)-2-Acetoxy-exo-3-(N,N-dimethylamino-methyl)-bicyclo[2,2,1]heptane Hydrochloride



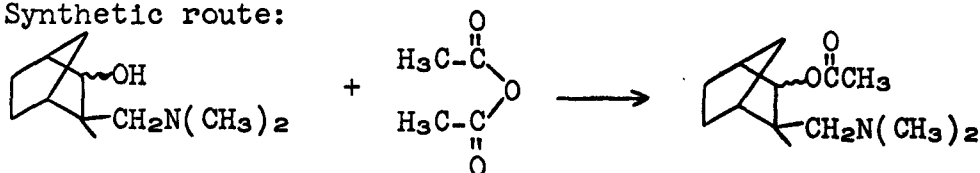
C₁₂H₂₂ClNO₂

Amount 1.0 g.

M.W. 247.77

M.P. 169-170° (corrected)

- b. Synthetic route:



3(N,N-Dimethylaminomethyl)-bicyclo[2,2,1]heptanol-2 (a mixture of endo and exo) was heated on a steam bath with a 100% excess of acetic anhydride for 7.5 hours. The cooled reaction mixture was poured into water, saturated with potassium carbonate and potassium hydroxide and extracted into ether. The dried ether extracts were evaporated and the residues distilled under reduced pressure. The ester was converted to the hydrochloride salt in ethyl ether and purified by recrystallization from acetonitrile.

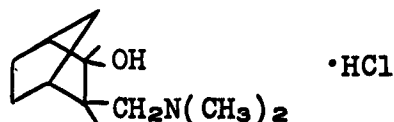
- c. Purity was determined by infrared spectroscopy and nitrogen analysis in these laboratories and by carbon and hydrogen assay performed by Weiler and Strauss.

Anal. Calcd. for C, 58.15; H, 8.95; N, 5.66.
Found: C, 58.63; H, 8.89; N, 5.77.

- d. Equipment utilized was conventional Pyrex standard taper laboratory glassware.

Data Sheet for Compound No. 7121-37
Lakeside Laboratories, Reference No. RB 1078-51; EX 10-445

a. endo-2-Hydroxy-exo-3-(N,N-dimethylaminomethyl)-bicyclo[2,2,1]-heptane Hydrochloride



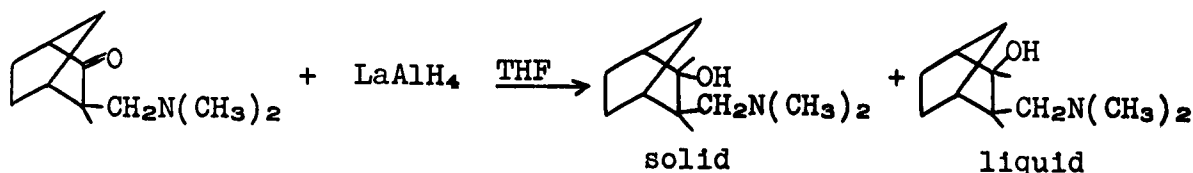
$\text{C}_{10}\text{H}_{20}\text{ClNO}$

Amount 1.0 g.

M. W. 205.73

M. P. 222-223°C

b. Synthetic route:



3-(N,N-Dimethylaminomethyl)-bicyclo[2,2,1]heptanone-2 was reduced with lithium aluminum hydride in refluxing tetrahydrofuran. The isomeric forms of the alcohol were separated by fractional distillation through a Stedmann column. The hydrochloride salt was prepared in ethyl ether and recrystallized from acetonitrile.

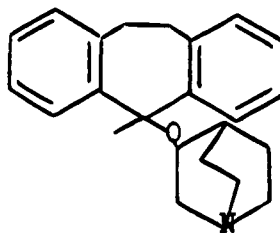
- c. Purity was determined by infrared spectroscopy in these laboratories and by carbon and hydrogen analysis performed by Weiler and Strauss. Configuration was determined by hydrogen bonding studies in the infrared.

Anal. Calcd. for $\text{C}_{10}\text{H}_{20}\text{ClNO}$: C, 58.38; H, 9.80.
Found: C, 58.46; H, 9.81.

- d. Equipment utilized was conventional Pyrex standard taper laboratory glassware.

Data Sheet for Compound No. 7121-38
Lakeside Laboratories, Reference No. RB 1078-53; EX 10-444

a. 5-(3-Quinuclidyloxy)-5H-dibenzo[a,d]cycloheptadiene



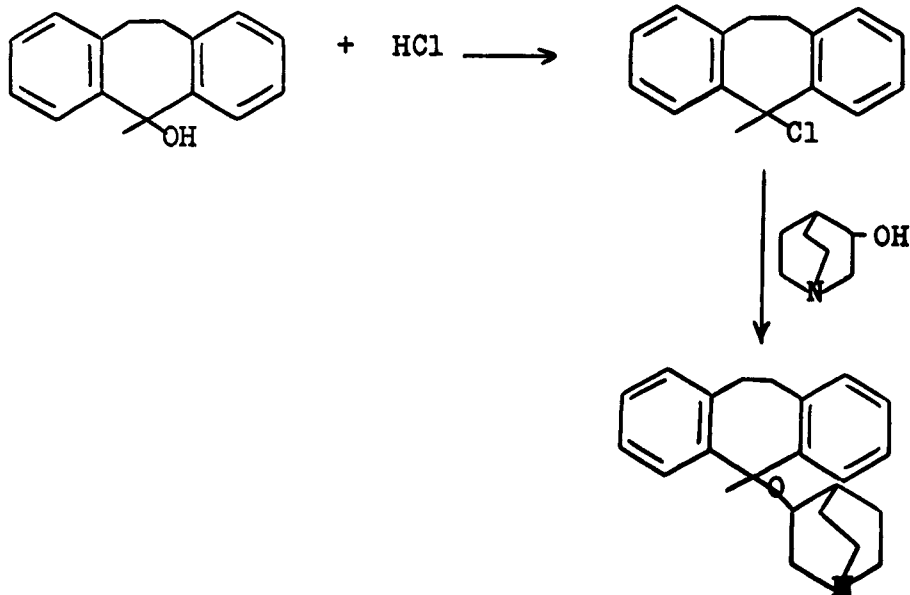
$C_{22}H_{25}NO$

Amount 1.0 g.

M. W. 319.428

M. P. 112-113°

b. Synthetic route:



Anhydrous hydrogen chloride was bubbled through a cooled benzene solution of 5-hydroxy-5H-dibenzo[a,d]cycloheptadiene. The resulting chloro derivative was added to a solution of 3-quinuclidinol in toluene, and the mixture was refluxed for six hours. The base was isolated and purified by distillation under reduced pressure and recrystallized from Skellysolve B.

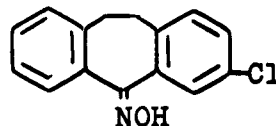
- c. Purity was determined by infrared spectroscopy in these laboratories and by carbon and hydrogen analysis performed by Weiler and Strauss.

Anal. Calcd. for $C_{22}H_{25}NO$: C, 82.78; H, 7.89.
Found: C, 82.75; H, 7.97.

- d. Equipment utilized was conventional Pyrex standard taper laboratory glassware.

Data Sheet for Compound No. 7121-39
Lakeside Laboratories, Reference No. 1076-193B, EX 10-457

a. 3-Chloro-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-one Oxime



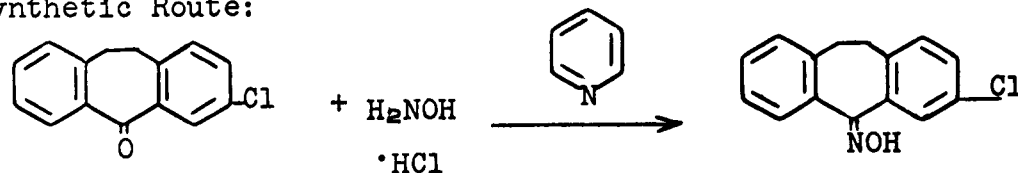
$C_{15}H_{12}ClNO$

Amount 1.0 Gram

M. W. 257.711

M. P. 197-200° (Corrected)

b. Synthetic Route:



The oxime was prepared according to the procedure reported by A. M. Monro, R. M. Quinton and T. J. Wrigley, J. Med. Chem., Volume 6, No. 3, P. 255-261 (1963), and was purified by recrystallization from acetonitrile.

- c. Purity was determined by infrared spectroscopy, nitrogen and chlorine analysis performed in these laboratories and by carbon and hydrogen assay by Weiler and Strauss.

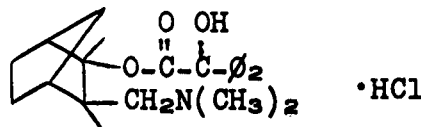
Anal. Calcd. for $C_{15}H_{12}ClNO$: C, 69.91; H, 4.70; N, 5.44; Cl, 13.76.
 Found: C, 69.91; H, 4.70; N, 5.34; Cl, 13.79.

- d. Equipment utilized was conventional Pyrex standard taper laboratory glassware.

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Data Sheet for Compound No. 7121-40
Lakeside Laboratories, Reference No. RB 1076-199A, EX 10-459

- a. endo-(2-Benzilyloxy)-exo-3-(N,N-dimethylaminomethyl)-bicyclo[2,2,1]heptane Hydrochloride



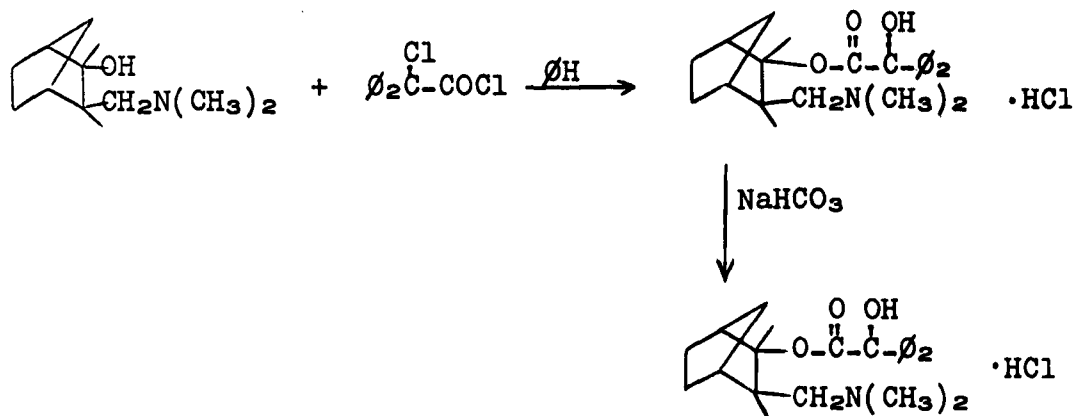
$C_{24}H_{30}ClNO_3$

Amount 1.0 Gram

M. W. 415.945

M. P. 147-148° (Corrected)

- b. Synthetic Route:



Endo-2-hydroxy-exo-3-(N,N-dimethylaminomethyl)-bicyclo[2,2,1]heptane was allowed to react with α -chlorodiphenylacetyl chloride in refluxing benzene for 3.5 hours. The resulting crude α -chloro derivative of the ester hydrochloride was then hydrolyzed to the desired α -hydroxy ester in aqueous $NaHCO_3$. The basic ester was partially purified by trituration in Skelly B, converted to the hydrochloride salt in ethyl ether and purified by recrystallization from isopropanol.

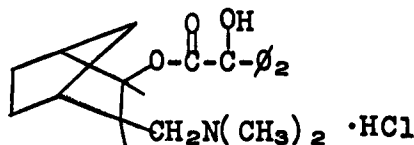
- c. Purity was determined by infrared spectroscopy and by carbon, hydrogen and oxygen analysis performed at the Army Chemical Center.
- d. Equipment utilized was conventional Pyrex standard taper laboratory glassware.

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Data Sheet for Compound No. 7121-41
Lakeside Laboratories, Reference No. RB 1076-205F, EX 10-461

- a. exo-2-(Benzilyloxy)-exo-3-(N,N-dimethylaminomethyl)-bicyclo[2,2,1]heptane Hydrochloride



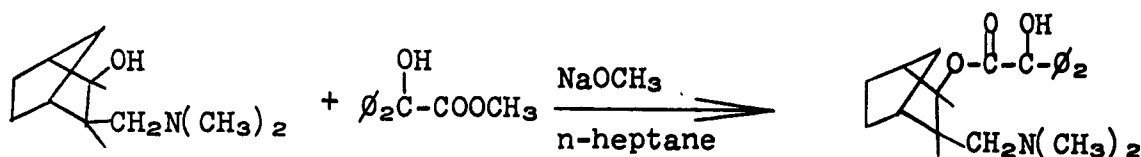
$C_{24}H_{30}ClNO_3$

Amount 1.0 gram

M. W. 415.9

M. P. 198-200° (Corrected)

- b. Synthetic Route:



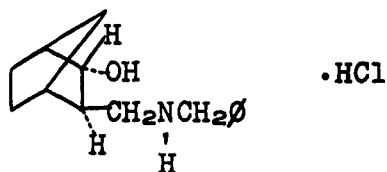
exo-2-Hydroxy-exo-3-(N,N-dimethylaminomethyl)-bicyclo[2,2,1]heptane was transesterified with methyl benzilate in refluxing n-heptane in the presence of freshly prepared sodium methoxide. The ester was isolated as the hydrochloride salt and purified by recrystallization from isopropanol.

- c. Purity was determined by infrared spectroscopy in these laboratories and by carbon, hydrogen and oxygen analysis performed at the Edgewood Arsenal.
- d. Equipment utilized was conventional Pyrex standard taper laboratory glassware.

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Data Sheet for Compound 7121-42
Lakeside Laboratories, Reference No. RB 1078-103; EX 10-463

a. endo-2-Hydroxy-exo-3(N-benzylaminomethyl)bicyclo[2,2,1]heptane Hydrochloride



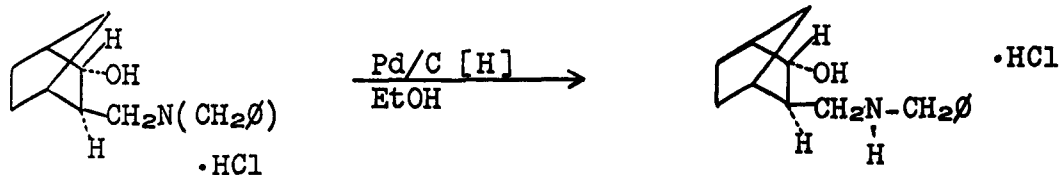
$C_{15}H_{22}ClNO$

Amount 1.0 g.

M. W. 267.80

M. P. 254-255° (corrected)

b. Synthetic route:



An ethanolic solution of endo-2-hydroxy-exo-3(N,N-dibenzylamino-methyl)bicyclo[2,2,1]heptane hydrochloride was debenzylated in the Parr Hydrogenation Apparatus in the presence of 10% palladium on carbon at 60 PSI H_2 . The catalyst was removed by filtration and the mother liquors evaporated under reduced pressure and the residues purified by recrystallization from acetonitrile.

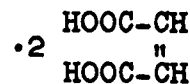
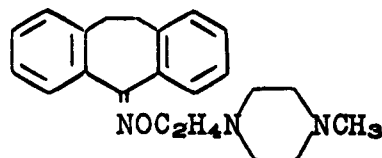
c. Purity was determined by infrared spectroscopy in these laboratories and by carbon, hydrogen and nitrogen analysis by Weiler and Strauss.

Anal. Calcd. for $C_{15}H_{22}ClNO$: C, 67.27; H, 8.28; N, 5.23.
Found: C, 67.43; H, 8.18; N, 5.45.

d. Equipment utilized was a Parr Low-Pressure Hydrogenation Apparatus and conventional Pyrex standard taper laboratory glassware.

Data Sheet for Compound 7121-43
Lakeside Laboratories, Reference No. RB 1076-225D, EX 10-464

a. O[β -(4-Methyl-1-piperazinyl)ethyl]-10,11-dihydro-5H-dibenzo[a,d]-cyclohepten-5-one Oxime Diacid Maleate



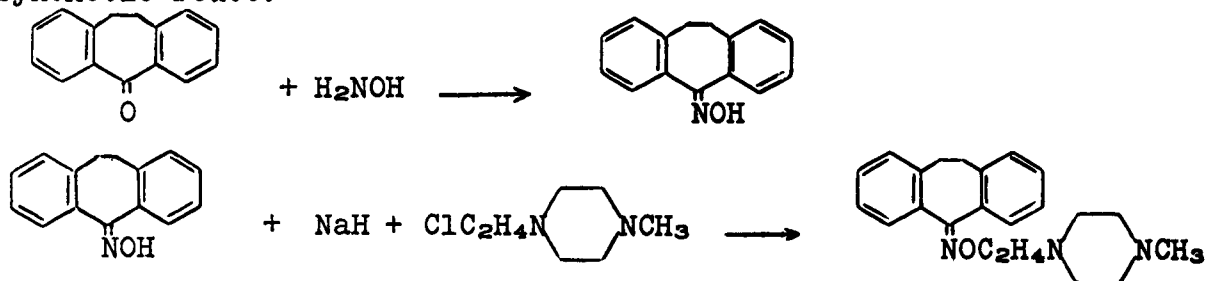
$\text{C}_{30}\text{H}_{35}\text{N}_3\text{O}_9$

Amount 1.0 g.

M. W. 581.604

M. P. 174-175° (corrected)

b. Synthetic route:



The oxime was prepared according to the procedure reported by A. M. Monro, R. M. Quinton and T. J. Wrigley, J. Med. Chem., Vol. 6, No. 3, p. 255-261 (1963). The oxime was alkylated using sodium hydride and 4-methyl-1-piperazinyl ethyl chloride in refluxing toluene. The diacid maleate salt was prepared from crude oxime and purified by recrystallization from ethanol.

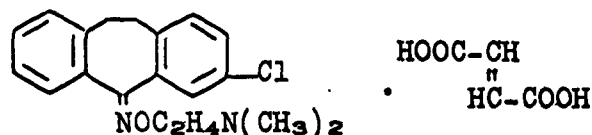
c. Purity was determined by infrared spectroscopy, nitrogen and neutral equivalent determinations in these laboratories and by carbon and hydrogen analysis by Weiler and Strauss.

Anal. Calcd. for $\text{C}_{30}\text{H}_{35}\text{N}_3\text{O}_9$: C, 61.95; H, 6.06; N, 7.24; NE, 145.4.
 Found: C, 61.98; H, 6.25; N, 7.27; NE, 146.0.

d. Equipment utilized was conventional Pyrex standard taper laboratory glassware.

Data Sheet for Compound 7121-44
Lakeside Laboratories, Reference No. RB 1076-277A, EX 10-465

- a. O[β -(N,N-Dimethylamino)ethyl]-3-chloro-10,11-dihydro-5H-dibenzo-
[a,d]cyclohepten-5-one Oxime Acid Fumarate



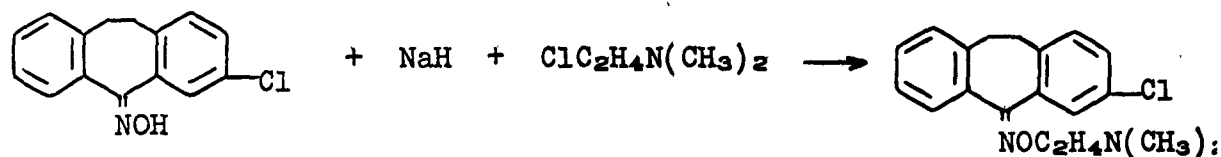
$C_{23}H_{25}ClN_2O_5$

Amount 1.0 g.

M. W. 444.903

M. P. 143-144° (corrected)

- b. Synthetic route:



The oxime was alkylated using sodium hydride and dimethylaminoethyl chloride in refluxing toluene. The acid fumarate was prepared in ethanol-ethyl ether and purified by recrystallization from isopropanol.

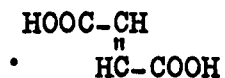
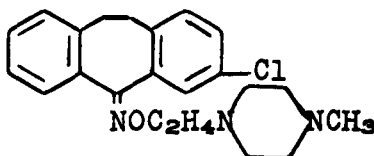
- c. Purity was determined by infrared spectroscopy, nitrogen and chlorine determinations in these laboratories and by carbon and hydrogen analysis by Weiler and Strauss.

Anal. Calcd. for $C_{23}H_{25}ClN_2O_5$: C, 62.08; H, 5.66; N, 6.30; Cl, 7.97.
Found: C, 62.25; H, 5.85; N, 6.23; Cl, 7.96.

- d. Equipment utilized was conventional Pyrex standard taper laboratory glassware.

Data Sheet for Compound 7121-45
Lakeside Laboratories, Reference No. RB 1076-277B, EX 10-466

- a. O[β -(4-Methyl-1-piperazinyl)ethyl]-3-chloro-10,11-dihydro-5H-dibenzol[a,d]cyclohepten-5-one Oxime Fumarate



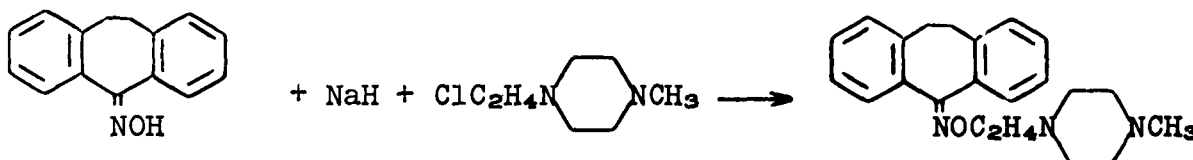
$\text{C}_{26}\text{H}_{30}\text{ClN}_3\text{O}_5$

Amount 1.0 g.

M. W. 499.981

M. P. 195-196° (corrected)

- b. Synthetic route:



The oxime was alkylated using sodium hydride and 4-methyl-1-piperazinyl ethyl chloride in refluxing toluene. The fumarate salt was prepared from the crude alkylated oxime in ethanol and purified by recrystallization from ethanol.

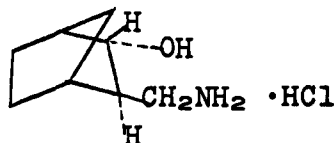
- c. Purity was determined by infrared spectroscopy, nitrogen and chlorine determinations in these laboratories and by carbon and hydrogen analysis by Weiler and Strauss.

Anal. Calcd. for $\text{C}_{26}\text{H}_{30}\text{ClN}_3\text{O}_5$: C, 62.45; H, 6.05; N, 8.40; Cl, 7.09.
 Found: C, 62.45; H, 6.14; N, 8.42; Cl, 7.01.

- d. Equipment utilized was conventional Pyrex standard taper laboratory glassware.

Data Sheet for Compound No. 7121-46
Lakeside Laboratories, Reference No. RB 1078-113; EX 10-470

a. endo-2-Hydroxy-exo-3(aminomethyl)-bicyclo[2,2,1]heptane Hydrochloride



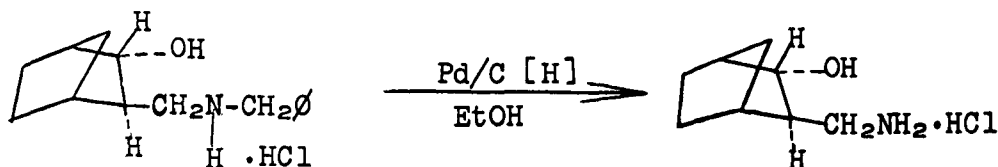
$C_8H_{16}ClNO$

Amount 1.0 gram

M.W. 177.68

M.P. 245° (corrected)

b. Synthetic route:



An aqueous ethanolic solution of endo-2-hydroxy-exo-3-N-benzylaminomethyl)-bicyclo[2.2.1]heptane hydrochloride was debenzylated in the Parr Hydrogenation Apparatus in the presence of 10% palladium on carbon at 60 PSI H_2 at 40°C. The catalyst was removed by filtration and the mother liquors evaporated under reduced pressure and the residues purified by recrystallization from ethanol-ethyl ether.

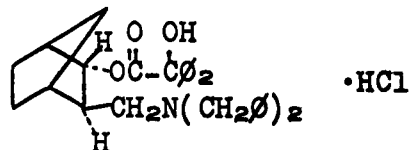
- c. Purity was determined by infrared spectroscopy, nitrogen and chlorine determinations in these laboratories and by carbon and hydrogen analysis by Weiler and Strauss.

Anal. Calcd. for $C_8H_{16}ClNO$: C, 54.07; H, 9.02; N, 7.89; Cl, 19.97
 C, 54.20; H, 9.00; N, 7.78; Cl, 19.51

- d. Equipment utilized was a Parr Low-Pressure Hydrogenation Apparatus and conventional Pyrex standard taper laboratory glassware.

Data Sheet for Compound No. 7121-47
Lakeside Laboratories, Reference No. RB 1076-235D; EX 10-471

a. endo-2-Benzilyloxy-exo-3-(N,N-dibenzylaminomethyl)bicyclo[2,2,1]-heptane Hydrochloride



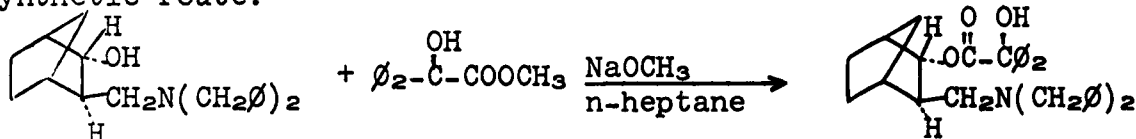
$C_{36}H_{38}ClNO_3$

Amount 1.0 gram

M. W. 568.129

M. P. 210-211° (corrected)

b. Synthetic route:



endo-2-Hydroxy-exo-3-(N,N-dibenzylaminomethyl)-bicyclo[2,2,1]heptane was transesterified with methyl benzoate in refluxing n-heptane in the presence of sodium methoxide. The ester was isolated as the hydrochloride derivative and purified by recrystallization from ethanol.

c. Purity was determined by infrared spectroscopy, nitrogen and chlorine determinations in these laboratories and by carbon and hydrogen analysis at the Edgewood Arsenal.

Anal. Calcd. for $C_{36}H_{38}ClNO_3$: C, 76.11; H, 6.74; N, 2.47; Cl, 6.24.
 Found: C, 76.2; H, 6.6; N, 2.52; Cl, 6.36.

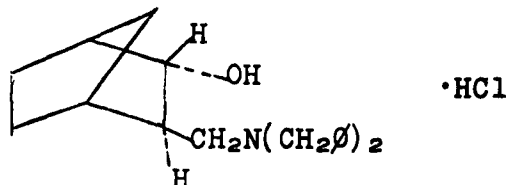
d. Equipment utilized was conventional Pyrex standard taper laboratory glassware.

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Data Sheet for Compound No. 7121-48

Lakeside Laboratories, Reference No. RB 1078-137A, EX 10-481

a. endo-2-Hydroxy-exo-3-(N,N-dibenzylaminomethyl)-bicyclo[2.2.1]-heptane hydrochloride



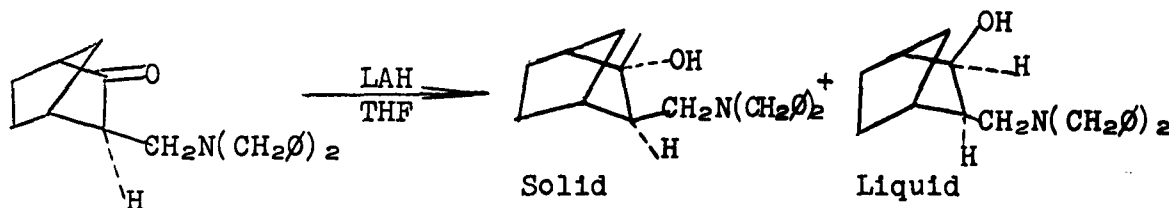
$\text{C}_{22}\text{H}_{28}\text{ClNO}$

Amount 1.0 g.

M.W. 357.93

M.P. 209-211°C (corrected)

b. Synthetic Route



3-(N,N-dibenzylaminomethyl)-bicyclo[2.2.1]heptanone-2 was reduced with lithium aluminum hydride in refluxing tetrahydrofuran. The product was purified by distillation of the isomer mixture. These distillates upon trituration with Skelly solve B afforded the solid isomer which was further purified by recrystallization from Skelly-solve B. The hydrochloride salt was prepared in ethyl ether and purified by recrystallization from ethyl acetate.

c. Purity was determined by infrared spectroscopy, nitrogen and chlorine determinations in these laboratories and by carbon and hydrogen analysis by Weiler and Strauss. Relative configuration was determined by hydrogen bonding studies in the infrared.

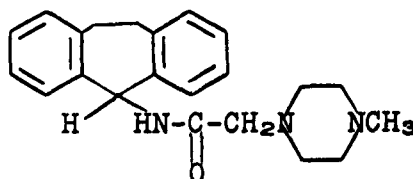
Anal. Calcd. for $\text{C}_{22}\text{H}_{28}\text{ClNO}$; C, 73.81; H, 7.88; N, 3.91; Cl, 9.90.
Found: C, 74.00; H, 8.04; N, 3.83; Cl, 9.72.

d. Equipment utilized was conventional Pyrex Standard taper laboratory glassware.

Data Sheet for Compound No. 7121-49

Lakeside Laboratories, Reference No. RB 1078-137B, EX 10-482

a. N-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-2-(4-methyl-piperazinyl)acetamide



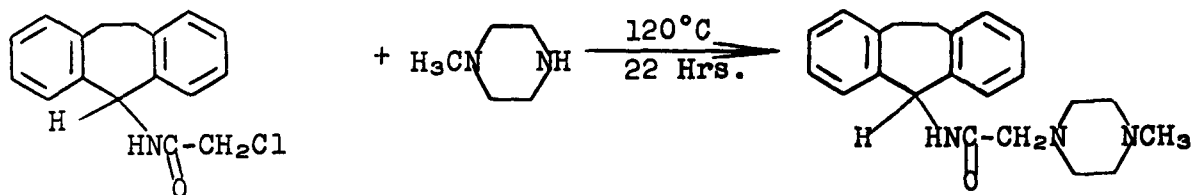
$C_{22}H_{27}N_3O$

Amount 1.0 g.

M.W. 349.48

M.P. 128-130°C (corrected)

b. Synthetic Route



A mixture of 2-chloro-N-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)acetamide and excess N-methyl piperazine in ethanol was heated in an autoclave at 120°C for 22 hours. The amide was purified by recrystallization from Skelly solve B.

Bernstein and losee, U.S. 3,052,721

c. Purity was determined by infrared spectroscopy in these laboratories and by carbon, hydrogen and nitrogen analysis by Weiler and Strauss.

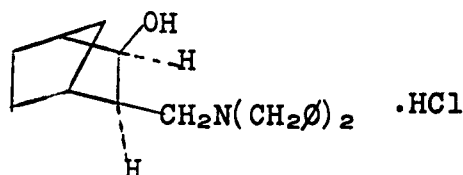
Anal. Calcd. for $C_{22}H_{27}N_3O$: C, 75.60; H, 7.64; N, 11.83,
Found: C, 75.36; H, 7.79; N, 12.03.

d. Equipment utilized was conventional Pyrex Standard taper laboratory glassware and a 300 ml. steel autoclave.

Data Sheet for Compound No. 7121-50

Lakeside Laboratories, Reference No. RB 1078-143, EX 10-486

a. exo-2-Hydroxy-exo-3-(N,N-dibenzylaminomethyl)-bicyclo-
[2.2.1]heptane hydrochloride



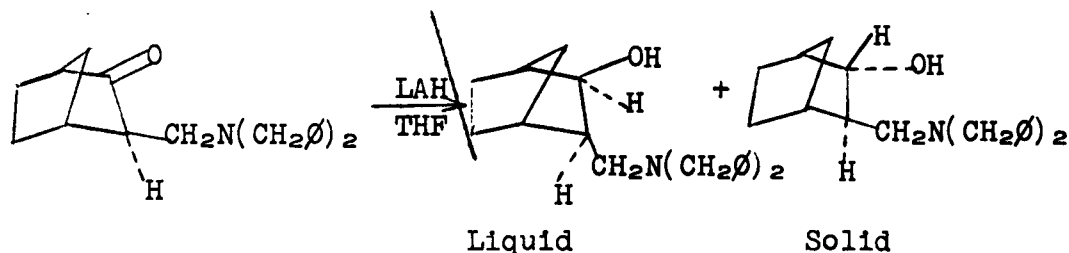
$\text{C}_{22}\text{H}_{28}\text{ClNO}$

Amount 1.0 g.

M.W. 357.93

M.P. 200-203°C (corrected)

b. Synthetic Route.



3-(N,N-dibenzylaminomethyl)-bicyclo[2.2.1] heptanone-2 was reduced with lithium aluminum hydride in refluxing tetrahydrofuran. The product was purified by distillation of the isomer mixture. These distillates upon trituration with Skelly solve B afforded the solid isomer which could be further purified by recrystallization from Skelly solve B. Upon evaporation of the Skelly solve mother liquors, a mixture of the liquid and solid isomers was obtained which could be purified by the formation of the hydrochloride salt in ether. The salt was further purified by recrystallization from ethyl acetate.

- c. Purity was determined by infrared spectroscopy, nitrogen and chlorine determinations in these laboratories and by carbon and hydrogen analysis by Weiler and Strauss. Relative configuration was determined by hydrogen bonding studies in the infrared.

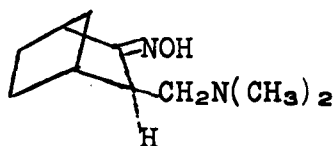
Anal. Calcd. for $\text{C}_{22}\text{H}_{28}\text{ClNO}$: C, 73.81; H, 7.88; N, 3.91; Cl, 9.90.
Found: C, 73.48; H, 7.75; N, 3.88; Cl, 9.92.

- d. Equipment utilized was conventional Pyrex Standard taper laboratory glassware.

Data Sheet for Compound 7121-51

Lakeside Laboratories, Reference No. RB 1076-269C, EX 10-485

a. exo-3-(N,N-Dimethylaminomethyl)-bicyclo[2.2.1]heptan-2-one
oxime



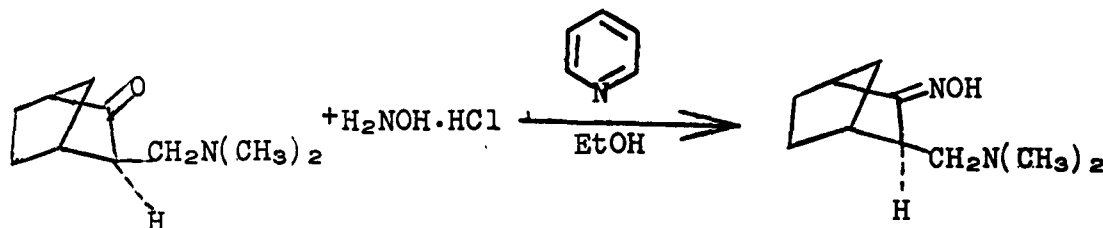
$C_{10}H_{18}N_2O$

Amount 1.0 g.

M.W. 182.26

M.P. 204-205° (corrected)

b. Synthetic Route



A mixture of 3-(N,N-dimethylaminomethyl)-bicyclo[2.2.1]heptan-2-one, hydroxylamine hydrochloride and pyridine were refluxed in ethanol for two hours. The oxime was purified by recrystallization from ethanol.

- c. Purity was determined by infrared spectroscopy and nitrogen determination in these laboratories and by carbon and hydrogen analysis by Weiler and Strauss.

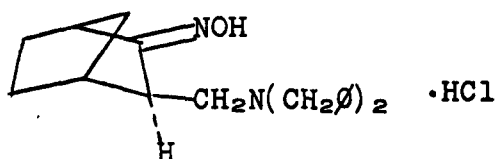
Anal. Calcd. for $C_{10}H_{18}N_2O$: C, 65.88; H, 9.95; N, 15.37.
Found: C, 65.95; H, 10.22; N, 15.50.

- d. Equipment utilized was conventional Pyrex Standard taper laboratory glassware.

Data Sheet for Compound No. 7121-52

Lakeside Laboratories, Reference No. RB 1076-275A, EX 10-488

a. exo-3-(N,N-Dibenzylaminomethyl)-bicyclo[2.2.1]heptanone-2-oxime hydrochloride



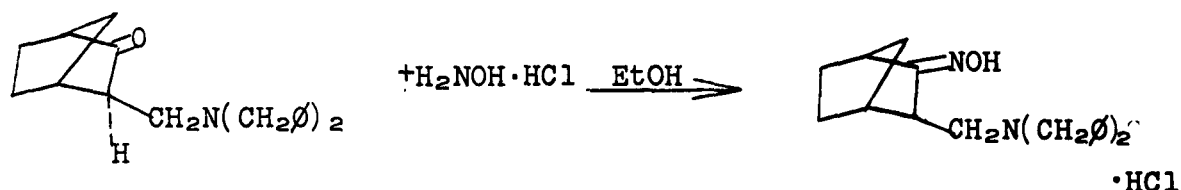
$C_{22}H_{27}ClN_2O$

Amount 1.0 g.

M.W. 370.909

M.P. 219-220°C (d) (corrected)

b. Synthetic Route



A mixture of 3-(N,N-dibenzylaminomethyl)-bicyclo[2.2.1]heptanone-2 and hydroxylamine hydrochloride was refluxed in ethanol for two hours. The amino oxime hydrochloride was purified by recrystallization from isopropanol.

- c. Purity was determined by infrared spectroscopy, nitrogen and chlorine determinations in these laboratories and by carbon and hydrogen analysis by Weiler and Strauss.

Anal. Calc'd for $C_{22}H_{27}ClN_2O$: C, 71.24; H, 7.34; N, 7.55; Cl, 9.56.
Found: C, 71.37; H, 7.44; N, 7.45; Cl, 9.62.

- d. Equipment utilized was conventional Pyrex Standard taper laboratory glassware.

Data Sheet for Compound 7121-53
Lakeside Laboratories, Reference No. RB 1095-7A; EX 10-503

a. endo-2-Benzilyloxy-exo-3-aminomethyl bicyclo[2,2,1]-heptane



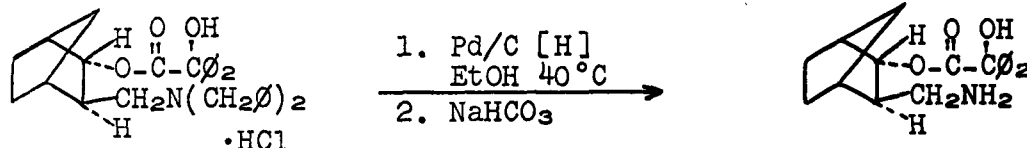
$C_{22}H_{25}NO_3$

Amount 1.0 gram

M. W. 351.428

M. P. 123-124°C (corrected)

b. Synthetic route:



An ethanolic solution of endo-2-benzilyloxy-exo-3-(N,N-dibenzylaminomethyl)-bicyclo[2,2,1]heptane hydrochloride was debenzylated in the Parr Hydrogenation apparatus in the presence of 10% palladium on carbon and hydrogen at a pressure of 60 PSI at 40°C. The catalyst was removed by filtration and the mother liquors were evaporated under reduced pressure and treated with aqueous sodium bicarbonate and the base extracted into ethyl ether. The dried ether solutions were evaporated under reduced pressure and the compound was purified by recrystallization from hot n-heptane.

c. Purity was determined by infrared spectroscopy and nitrogen determination in these laboratories and by carbon and hydrogen analyses performed at the Edgewood Arsenal.

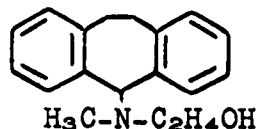
Anal. Calcd. for $C_{22}H_{25}NO_3$: N, 3.99. Found: N, 3.79.

d. Equipment utilized was a Parr Low-Pressure Hydrogenation Apparatus and conventional Pyrex standard taper laboratory glassware.

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Data Sheet for Compound 7121-54
Lakeside Laboratories, Reference No. RB 1078-169, EX 10-501

- a. 5-[N-Methyl-N-(2-hydroxy-1-ethyl)amino]-10,11-dihydro-5H-dibenzo-[a,d]cycloheptene



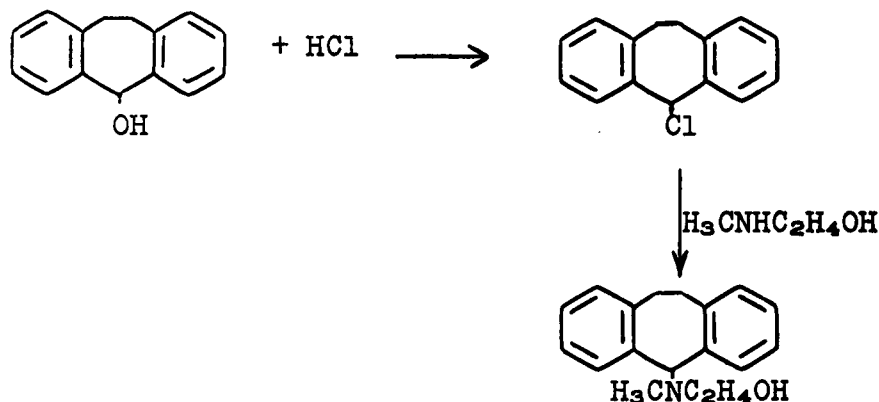
$\text{C}_{18}\text{H}_{21}\text{NO}$

Amount 1.0 gram

M. W. 267.376

B. P. 170-175°/0.04 mm.

- b. Synthetic route:



Anhydrous hydrogen chloride was bubbled through a cooled benzene solution of 10,11-dihydro-5H-dibenzo[a,d]cycloheptan-5-ol. The resulting chloro-compound was added to a solution of excess 2-methylaminoethanol in benzene, and the mixture was refluxed for six hours. The aminoalcohol was purified by distillation.

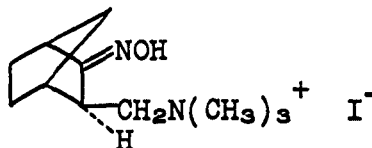
- c. Purity was determined by infrared spectroscopy and nitrogen determination in these laboratories and by carbon and hydrogen analysis by Weiler and Strauss.

Anal. Calcd. for $\text{C}_{18}\text{H}_{21}\text{NO}$: C, 80.89; H, 7.92; N, 5.24.
Found: C, 80.72; H, 8.19; N, 5.16.

- d. Equipment utilized was conventional Pyrex standard taper laboratory glassware.

Data Sheet for Compound 7121-55
Lakeside Laboratories, Reference No. RB 1076-291A, EX 10-500

- a. exo-3-(N,N-Dimethylaminomethyl)-bicyclo[2,2,1]-heptan-2-one oxime
Methyliodide



$C_{11}H_{21}N_2OI$

Amount 1.0 gram

M. W. 324.204

M. P. 249-250°(d)

- b. Synthetic route:

A mixture of exo-3-(N,N-dimethylaminomethyl)-bicyclo[2,2,1]-heptan-2-one oxime, methyl iodide and acetone was stirred at room temperature for sixteen hours. The resulting methyliodide salt was collected by filtration and purified by recrystallization from ethanol.

- c. Purity was determined by infrared spectroscopy in these laboratories and by carbon, hydrogen and nitrogen analysis by Weiler and Strauss.

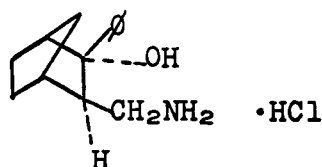
Anal. Calcd. for $C_{11}H_{22}N_2OI$: C, 40.74; H, 6.53; N, 8.65.
Found: C, 40.85; H, 6.52; N, 8.66.

- d. Equipment utilized was conventional Pyrex standard taper laboratory glassware.

Data Sheet for Compound 7121-56

Lakeside Laboratories Reference No. RB 1095-23E, EX 10-513

a. endo-2-Hydroxy-2-phenyl-exo-3-aminomethyl bicyclo[2.2.1]heptane hydrochloride



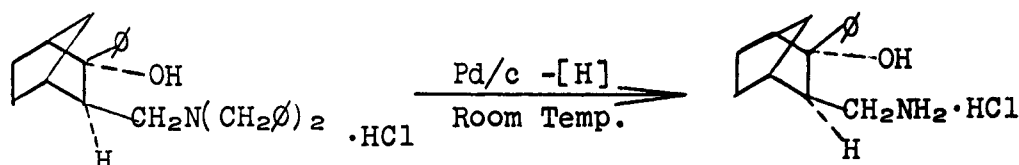
$C_{14}H_{20}ClNO$

Amount 1.0 gram

M.W. 253.765

M.P. 229-230°C(d) corrected

b. Synthetic route



A solution of endo-2-hydroxy-2-phenyl-exo-3-(N,N-dibenzylamino-methyl)-bicyclo[2.2.1]heptane hydrochloride in ethanol was reduced on the Parr Hydrogenation apparatus in the presence of 10% palladium on carbon and hydrogen at a pressure of 60 PSI at room temperature. The catalyst was removed by filtration and the mother liquors were evaporated under reduced pressure. The residues were purified by recrystallization from acetonitrile.

- c. Purity was determined by infrared spectroscopy, nitrogen and chlorine determinations in these laboratories and by carbon and hydrogen analysis by Weiler and Strauss.

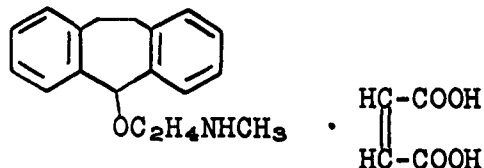
Anal. Calcd. for $C_{14}H_{20}ClNO$: C, 66.25; H, 7.94; Cl, 13.94; N, 5.52.
Found: C, 66.18; H, 7.96; Cl, 13.91; N, 5.51.

- d. Equipment utilized was a Parr Low-Pressure Hydrogenation apparatus and conventional Pyrex standard taper laboratory glassware.

Data Sheet for Compound 7121-57

Lakeside Laboratories Reference No. RB 1095-23F, EX 10-514

a. 5-[8-(N-Methylamino)ethoxy]-10,11-dihydro-5H-dibenzo[a,d]-cycloheptene acid maleate



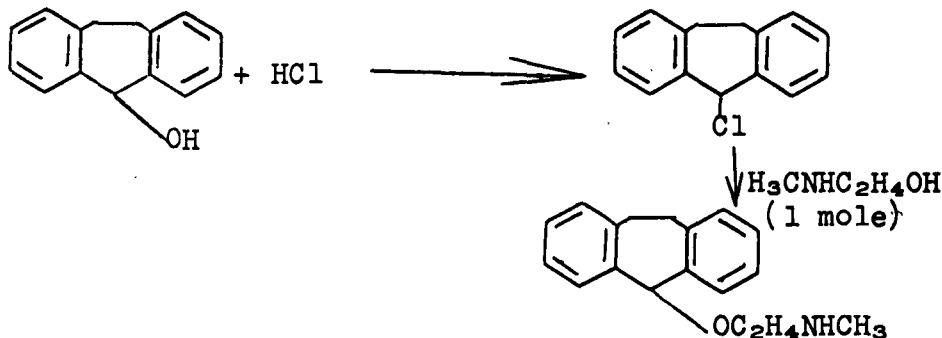
C₂₂H₂₅NO₅

Amount 1.0 gram

M.W. 383.428

M.P. 144-146°C (corrected)

b. Synthetic route



Anhydrous hydrogen chloride was bubbled through a cooled solution of 10,11-dihydro-5H-dibenzo[a,d]cyclohepten-2-ol and the resulting chloro derivative isolated and added in one portion to a solution of a stoichiometric amount of 2-methylaminoethanol in toluene. The mixture was stirred at reflux for six hours. The solids which formed were collected by filtration, released to the base and purified by fractionation under reduced pressure. The basic ether was converted to the maleic acid salt in ether and purified by recrystallization from ethyl acetate.

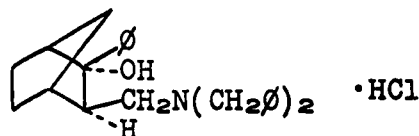
c. Purity was determined by infrared spectroscopy in these laboratories and by carbon, hydrogen and nitrogen analysis by Weiler and Strauss.

Anal. Calcd. for C₂₂H₂₅NO₅: C, 66.92; H, 6.57; N, 3.66.
Found: C, 66.79; H, 6.63; N, 3.43.

d. Equipment utilized was conventional Pyrex Standard taper laboratory glassware.

Data Sheet for Compound 7121-58
Lakeside Laboratories, Reference No. RB 1078-193A, EX 10-523

a. endo-2-Hydroxy-2-phenyl-exo-3-(N,N-dibenzylaminomethyl)-
-bicyclo[2,2,1]heptane Hydrochloride



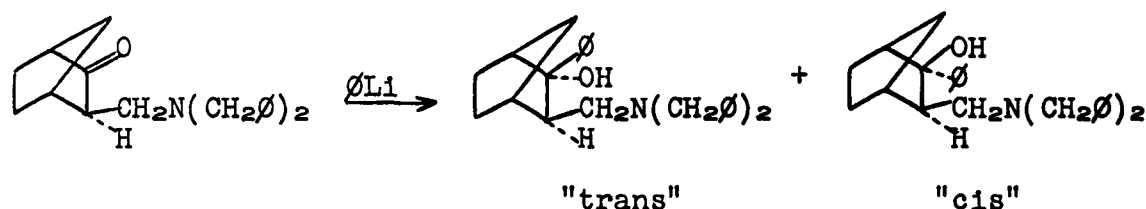
$C_{28}H_{32}ClNO$

Amount 1.0 g.

M. W. 434.03

M. P. 133-136°

b. Synthetic Route:



3-(N,N-Dibenzylaminomethyl)-bicyclo[2,2,1]heptan-2-one was allowed to react with phenyl lithium in tetrahydrofuran at room temperature. The isolated mixture of isomers (predominantly trans) was converted to the mixture of the hydrochloride salts in ether which were recrystallized from acetonitrile. The solids thus obtained were used for further experimental work (debenzylation studies).

Additional material was obtained by evaporating the mother liquors and suspending the residues in benzene. The benzene insoluble materials were purified by recrystallization from ethyl acetate yielding the pure trans isomer. The benzene soluble fractions are being retained for possible isolation of the cis isomer.

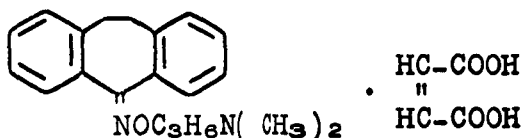
c. Purity was determined by infrared spectroscopy and nitrogen determination in these laboratories and by carbon and hydrogen analysis by Weiler and Strauss. Relative configuration was determined by hydrogen bonding studies in the infrared.

Anal. Calcd. for $C_{28}H_{32}ClNO$: C, 77.48; H, 7.20; N, 3.23.
Found: C, 77.25; H, 7.60; N, 3.19.

- d. Equipment utilized was conventional Pyrex standard taper laboratory glassware.

Data Sheet for Compound ACC 7121-59
Lakeside Laboratories, Reference No., RB 1095-37A, EX 10-533

- a. O-[γ-(N,N-Dimethylamino)propyl]-10,11-dihydro-5H-dibenzo-[a,d]cyclohepten-5-one oxime Acid Maleate



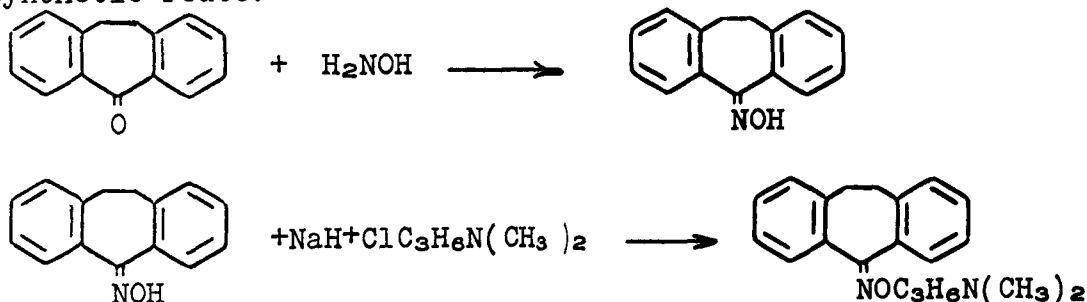
$C_{24}H_{28}N_2O_5$

Amount 1.0 g.

M. W. 424.480

M. P. 124-126° (corrected)

- b. Synthetic route:



The oxime was prepared according to the procedure reported by A. M. Monro, R. M. Quinton and T. J. Wrigley, J. Med. Chem., Vol. 6, No. 3, p. 251-261, (1963). The oxime was alkylated using sodium hydride and γ-N,N-dimethylaminopropyl chloride in refluxing toluene. The acid maleate was prepared from crude oxime and purified by recrystallization from ethyl acetate.

- c. Purity was determined by infrared spectroscopy in these laboratories and by carbon, hydrogen and nitrogen analysis by the Schwarzkopf Microanalytical Laboratories.

Anal. Calcd. for $C_{24}H_{28}N_2O_5$: C, 67.90; H, 6.65; N, 6.60.
 Found: C, 67.52; H, 6.91; N, 6.58.

- d. Equipment utilized was conventional Pyrex standard taper laboratory glassware.

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AGENTS - C. I. Judd, Helen A. Leiser, J. LaFrentz,
W. Hoya

SECRET

Final Report, 19 Oct 64, pp - 8 tables
Contract DA 18-108-CML-7121

1. Incapacitating Agents
2. Contract DA 18-108-CML-7121

Final report describing accomplishments with respect to: (1) the synthesis of new esters of 3-hydroxyquinuclidine; (2) synthesis of new bicyclic aminoalcohols and benzilate esters thereof; (3) synthesis of basic derivatives of 5-substituted dibenzo[a,d]cyclobutenes; and (4) investigations for the resolution of phenylcyclopentylglycolic acid.

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